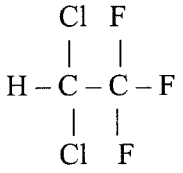
The studies listed below were selected to represent the best available study design and execution for these HPV toxicity endpoints. Other data of equal or lesser quality are not summarized, but are listed as related references in this document.

1.0 Substance Information

CAS Number: 306-83-2

Chemical Name: Ethane, 2,2-dichloro-1,1,1-trifluoro-

Structural Formula:



Other Names:
1,1,1-Trifluoro-2,2-dichloroethane
1,1,1-Trifluorodichloroethane
1,1-Dichloro-2,2,2-trifluoroethane
Dichloro(trifluoromethyl)methane
CFC 123
Chlorofluorocarbon 123
F 123
F 123 (halocarbon)
FC 123
Freon® 123
Fron 123
HCFC-123
HFA 123
Hydrochlorofluorocarbon
R 123
Refrigerant HCFC-123
Refrigerant R 123
Solkane 123
SUVA® 123

Exposure Limits:	50 ppm, 8-hour TWA: AIHA Workplace Environmental Exposure Limit (WEEL) 1000 ppm for up to 60 minutes with a 1 minute not-to-exceed ceiling of 2500 ppm. DuPont Emergency Exposure Limits (EEL) are established to facilitate site or plant emergency evacuation and specify airborne concentrations of brief duration that should not result in permanent adverse health effects or interfere with escape.

2.0 Physical/Chemical Properties

2.1 Melting Point

Value:	-107°C
Decomposition:	No
Sublimation:	No
Pressure:	1 atm
Method:	Unknown
GLP:	Unknown
Reference:	DuPont Co. Unpublished Data.
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point: None Found.

2.2 Boiling Point

Value:	27.8°C
Decomposition:	No Data
Pressure:	760 mm Hg
Method:	No Data
GLP:	Unknown
Reference:	Goodwin et al. (1992). Int. J. Thermodynamics, 13(6):999-1009.
Reliability:	High because a scientifically defensible or guidelined method was used.

Additional References for Boiling Point: None Found.

2.3 Density

Value:	Liquid Density = 1.45 g/cm^3 Vapor Density = 5.3 (Air = 1.0)
Temperature:	25°C for liquid density
Method:	No Data

GLP:	Unknown
Results:	No additional data.
Reference:	DuPont Co. (2001). Material Safety Data Sheet No. DU002798 (June 16).
	DuPont Co. Unpublished Data.
Reliability:	Not assignable because limited study information was available.

Additional References for Density: None Found.

2.4 Vapor Pressure

Value:	13.24 psia (706 mm Hg)
Temperature:	25°C
Decomposition:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Goodwin et al. (1992). Int. J. Thermodynamics, 13(6):999-1009.
Reliability:	High because a scientifically defensible or guidelined method was used.

Additional References for Vapor Pressure: None Found.

2.5 Partition Coefficient (log Kow)

Value:	2.307
Temperature:	No Data
Method:	No Data
GLP:	Unknown
Reference:	U. S. EPA (1988). PCGEMS and CLOGP (HSDB/6752).
	Lyman, W. J. et al. (1982). Handbook of Chemical Property Estimation Methods, McGraw-Hill, New York (HSDB/6752).
Reliability:	Estimated value based on accepted model.

Additional Reference for Partition Coefficient (log Kow):

Leo, A. J. (1982). LogP Values Calculated Using the CLOGP Program for Compounds in ISHOW Files, Pomona College Medicinal Chemistry Project, Seaver Chemistry Laboratory, Claremont, CA (ISHOW/IS-0007868).

2.6 Water Solubility

Value:	1488 mg/L
Temperature:	25°C
pH/pKa:	No Data
Method:	Estimated
GLP:	Unknown
Reference:	Lyman, W. J. et al. (1982). Handbook of Chemical Property Estimation Methods, Chapters 4 & 15, McGraw-Hill, New York (HSDB/6752).
Reliability:	Estimated value based on accepted model.

Additional References for Water Solubility:

DuPont Co. (2001). Material Safety Data Sheet No. DU002798 (June 16).

Horvath, A. L. et al. (1999). IUPAC-NIST Solubility Data Series 67, J. Phys. Chem. Ref Data, 28:395-627.

Meylan, W. M. and P. H. Howard (1991). Environ. Toxicol. Chem., 10:1283-93 (HSDB/6752).

US EPA (1988). PCGEMS and CLOGP (HSDB/6752).

2.7 Flash Point

Value:	None
Method:	TAG Closed Cup
GLP:	Unknown
Reference:	DuPont Co. Unpublished Data.
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point: None Found.

2.8 Flammability

Results:	Not Applicable
Method:	Not Applicable
GLP:	Not Applicable
Reference:	DuPont Co. (2001). Material Safety Data Sheet No. DU002798 (June 16).
Reliability:	Not assignable because limited study information was available.

Additional Reference for Flammability:

Burns, T. H. S. et al. (1982). Anaesthesia, 37:278-284.

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	Not Applicable
Temperature:	Not Applicable
Direct Photolysis:	Not Applicable
Indirect Photolysis:	Not Applicable
Breakdown Products:	Not Applicable
Method:	Experimental rate constants for the gas-phase reaction of HCFC-123 with photochemically produced hydroxyl radicals of $1.4x10^{-14}cm^3$/molec-sec (Cohen and Benson, 1987a; 1987b) and $5.9x10^{-14}$ cm^3/molec-sec at 303°K (Brown et al., 1990) have been reported. The recommended value of $3.35x10^{-14}$ cm^3/molec-sec (Atkinson, 1989) translates to an atmospheric half-life of 479 days using an average atmospheric hydroxyl radical concentration of $5x10^5$ molecules/cm^3 (Atkinson, 1989). HCFC-123 is removed predominately in the lower troposphere due to the reaction with the hydroxyl radical (Rattigan et al., 1993). The calculated atmospheric lifetime for HCFC-123 ranges from 1.2-2.4 years (Fisher et al., 1990; Carasiti et al., 1997).
GLP:	Not Applicable
Reference:	Cohen, N. and S. W. Benson (1987a). J. Phys. Chem., 91:162-70 (HSDB/6752). Cohen, N. and S. W. Benson (1987b). J. Phys. Chem., 91:171-5 (HSDB/6752). Brown, A. C. et al. (1990). Atmos. Environ., 24A: 2499-511 (HSDB/6752). Atkinson, R. (1989). J. Chem. Phys. Ref. Data Monograph (HSDB/6752). Fisher, D. A. et al. (1990). Nature, 344:508-512 (HSDB/6752). Rattigan, O. et al. (1993). SPA-AFEAS Final report (P91-069). Carassiti, V. et al. (1997). J. Environ. Path. Toxicol. Oncol.,

16(2&3):85-91.
Reliability: Estimated value based on accepted model.

Additional Reference for Photodegradation:

Data from this additional source support the study results summarized above. The study was not chosen for detailed summarization because the data were not substantially additive to the database.

ECETOC Joint Assessment of Commodity Chemicals (1996). Vol. 33 (TOXLINE/1998/123611).

3.2 Stability in Water

Concentration: Not Applicable
Half-life: Not Applicable
% Hydrolyzed: Not Applicable
Method: If removed from the atmosphere by wet deposition processes or released to water, HCFC-123 will rapidly volatilize to the atmosphere (Meylan and Howard, 1991; SRC, n.d.). The estimated half-lives for volatilization from a model river (1 m deep, flowing 1 m/sec, wind velocity of 3 m/sec) and model lake (1 m deep, flowing 0.05 m/sec, wind velocity of 0.5 m/sec) are 3.6 hours (Lyman et al., 1982) and 118 hours, respectively (SRC EpiWin 3.05). An estimated soil adsorption coefficient of 430 (Meylan and Howard, 1991; Lyman et al., 1982; US EPA, 1988) indicates that this chemical will not adsorb to sediment or suspended organic matter (SRC, n.d.).
GLP: Not Applicable
Reference: Meylan, W. M. and P. H. Howard (1991). Environ. Toxicol. Chem., 10:1283-93 (HSDB/6752).

Lyman, W. J. et al. (1982). Handbook of Chemical Property Estimation Methods, McGraw-Hill, New York (HSDB/6752).

SRC (n.d.). Syracuse Research Corporation (HSDB/6752).

SRC EpiWin 3.05.

US EPA (1988). PCGEMS and CLOGP (HSDB/6752).
Reliability: Estimated value based on accepted model.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity):

Media:	Air, Water, Soil, Sediment
Distributions:	Air: 99.8% Water: 0.121 % Soil: 0.0426% Sediment: 6.86E-4%
Adsorption Coefficient:	Not Applicable
Desorption:	Not Applicable
Volatility:	Not Applicable
Method:	Calculated according to Mackay, Level III, Syracuse Research Corporation Epiwin Version 3.05. Emissions (1000 kg/hr) to air using EPA model defaults. Data Used: Molecular Weight: 152.93 Henry's Law Constant: 0.0256 atm-m^3/mole (Exp value) Vapor Pressure: 706 mm Hg (Exp value) Log Kow : 2.307 (U. S. EPA (1988). PCGEMS and CLOGP (HSDB/6752)). Soil Koc : 83.1 (calc by model)
GLP:	Not Applicable
Reference:	Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming approach was developed by Dr. Donald Mackay and co-workers which is detailed in: Mackay, D. (1991). Multimedia Environmental Models; The Fugacity Approach, pp. 67-183, Lewis Publishers, CRC Press. Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626. Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.
Reliability:	Estimated value based on accepted model.

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation

Value:	24% degradation HCFC-123 during the 28 day test.
Breakdown	Not Applicable

Products:	
Method:	OECD 301D Closed Bottle Test. HCFC-123, at a test concentration of 12.5 mg/L, was incubated in closed vials inoculated with an activated sludge culture obtained from a municipal wastewater treatment facility. Dissolved oxygen concentrations of duplicate vials were measured at the start of the experiment and after 5, 15, and 28 days at 20ºC.
GLP:	Yes
Reference:	Life Sciences Research (1992). Report 91/PFE008/0477 (also cited in TSCA Fiche OTS0546420).
Reliability:	High because a scientifically defensible or guidelined method was used.

Additional References for Biodegradation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

De Flaun, M. F. et al. (1992). Biotechnology, 10:1576-1578.

Berends, A. G. et al. (1999). Arch. Environ. Contam. Toxicol., 36(2):146-151 (CA130:233357).

Oremland, R. S. et al. (1996). Appl. Environ. Microbiol., 62(5):1818-1821 (TOXLINE/1996/69911).

Streger, S. H. et al. (1999). Environ. Sci. Technol., 33:4477-4482.

3.5 Bioconcentration

Value:	BCF = 33
Method:	The estimated value was calculated based on an estimated log Kow of 2.307 (U.S. EPA, 1988; Lyman et al., 1982). This value indicates that HCFC-123 will not bioconcentrate in fish or aquatic organisms (SRC, n.d.).
GLP:	Not Applicable
Reference:	U. S. EPA (1988). PCGEMS and CLOGP (HSDB/6752). Lyman, W. J. et al. (1982). Handbook of Chemical Property Estimation Methods, McGraw-Hill, New York (HSDB/6752). SRC (n.d.). Syracuse Research Corporation (HSDB/6752).
Reliability:	Estimated value based on accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Type:	**96-hour LC_{50}**
Species:	Rainbow trout, *Salmo gairdneri*
Value:	55.5 mg/L (mean measured concentration)
Method:	Groups of 10 fish were exposed to HCFC-123, in sealed vessels, at nominal concentrations of 13.3, 23.5, 42.5, 74.3, and 133 mg/L. The study was conducted under semi-static exposure conditions. Test media were individually prepared in glass aspirators by the direct addition of test material to dilution water and were renewed at 24-hour intervals. HCFC-123 was not easy to disperse so the contents of each aspirator were stirred for 3 hours after preparation to aid dissolution. A control group of fish was placed in dilution water alone. After 24, 48, and 72 hours, the surviving fish in each vessel were transferred to another vessel containing fresh dilution water. The test material was then added and the medium stirred for 3 hours. The test and control media were not aerated during the test. The pH was neither adjusted before the start of the test nor controlled during the test. Temperature, pH, and concentration of dissolved oxygen of the contents of each vessel were measured at the start of the test and then each day following observations of fish behavior. The total hardness of the water control and selected test dilutions were also determined. The fish were last fed 24 hours before the start of the test. The mean wet-weight of the fish was 2.0 g and the mean fork length was 5.4 cm. The day length in the test area was controlled giving a photoperiod of 16 hours light and 8 hours darkness. Exposure levels were monitored by gas chromatography. Duplicate samples were removed from each vessel approximately 3 and 24 hours after the addition of the test material on 2 occasions. Observations of the fish were made at least at 24-hour intervals during the test.
GLP:	Yes

(19-December-2001)

Test Substance: HCFC-123, purity not specified

Results: The test was conducted at 14.0±0.7°C in treated tap water of hardness 204 to 230 mg/L (as $CaCO_3$) and at pH 7.1-7.7. Dissolved oxygen ranged from 62-98% air saturation value (ASV). At all concentrations, the test media were clear and colorless. However, at 133 mg/L (nominal), a globule of test material was still visible 3 hours after preparation, but had disappeared after 24 hours.

At all levels except the highest (133 mg/L, nominal) intended concentrations were achieved and maintained (overall range 78-115% of nominal). At the highest level, the mean measured concentration was 68% of nominal. In the first 24 hours of the test, measured levels of HCFC-123 increased suggesting the slow dissolution rate of the material. Analytical results obtained at 75 and 96 hours were less consistent, but overall showed intended levels had been achieved and maintained. Overall, the "closed" system employed was effective at maintaining aqueous levels of the test material. The variation observed was not thought to have affected the integrity of the study since a clear concentration-related response was observed.

The highest nominal concentration at which no mortalities occurred and the lowest at which there was 100% mortality were 42.5 and 133 mg/L, respectively (mean measured concentrations, 33.3 and 90.6 mg/L). A single death at 13.3 mg/L was not considered treatment-related. The majority of deaths occurred within 24 hours at 133 mg/L (nominal) and within 48 hours at 74.3 mg/L (nominal).

Treatment-related effects were seen at all exposure levels. At 74.3 and 133 mg/L (nominal), all fish were affected within 4 hours and, during the course of the test, exhibited darkened pigmentation, lethargic behavior, and loss of coordination. At 13.3, 23.5, and 42.5 mg/L (nominal) respectively, 2, 3, and 4 fish were affected at the end of the test, exhibiting either darkened pigmentation or lethargic behavior. The no-observed effect concentration was <13.3 mg/L (mean measured concentration, 15.3 mg/L).

Mean lethal concentrations (nominal) at 24, 48, 72, and 96 hours were 83.5, 69.2, 65.4, and 65.4 mg/L, respectively. Mean lethal concentrations (measured) at 24, 48, 72, and 96 hours were 64.1, 59.4, 55.5, and 55.5 mg/L, respectively. The 48-, 72-, and 96-hour LC_{50} values were approximate

because the data did not permit statistically valid calculations. Since mortalities were not progressive during the test, an asymptotic LC_{50} was thought to have been attained.

Reference: Life Sciences Research (1992). Unpublished Data, Report 91/0939.

Reliability: High because a scientifically defensible or guidelined method was used.

Additional Reference for Acute Toxicity to Fish:

Data from this additional source supports the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1990). Unpublished Data, Haskell Laboratory Report No. 243-90 (also cited in TSCA Fiche OTS0530601 and OTS0539556).

4.2 Acute Toxicity to Invertebrates

Type: **48-hour EC_{50}**

Species: Daphnia magna

Value: 17.3 mg/L (95% confidence interval, 13.6-23.1 mg/L) (mean measured concentration)

Method: Groups of 20 *daphnia* were exposed to HCFC-123, in sealed vessels, at nominal concentrations of 3.47, 6.94, 13.9, 27.7, and 55.2 mg/L. The test media were made individually by dilution of aqueous stock solutions prepared in the test dilution water in a cold room (nominally 5ºC). Aqueous stock were shaken until all of the test material had disappeared before use. A control group was placed in dilution water alone.

The day length was controlled giving a photoperiod of 16 hours light and 8 hours darkness.

The test vessels were all glass vials of approximately 120 mL capacity sealed with a rubber septum and a metal cap. Each test vessel was completely filled with water and 5 *daphnia* were added. The bottles were then sealed, with care being taken to ensure that there was no airspace. An aliquot of the appropriate stock was injected into each test vessel which were again fitted with a hypodermic needle to allow the excess water to be displaced. Four vessels, each containing 5 animals, were employed for each test and control group. Two additional vessels were also established

at each concentration for use at the start of the test, samples for chemical analysis and water quality measurements were taken from these bottles.

The temperature, pH, and concentration of dissolved oxygen of the dilution water and preparations of test substance at each exposure concentration were measured at the start and end of the test. The total hardness and alkalinity of the dilution water control were measured at the start and end of the test. Exposure levels were monitored by a GC method of analysis at the start of the test and at 48 hours.

Observations of the *daphnia* were made after 24 and 48 hours of exposure.

GLP: Yes

Test Substance: HCFC-123, purity not specified

Results: The test was conducted at 20.6 ± 0.2ºC in treated tap water of hardness 214 to 236 mg/L (as $CaCO_3$) and at pH values in the range of 7.7-8.0. Dissolved oxygen was 91-98% air saturation value and alkalinity was 140-150 mg/L as $CaCO_3$.

Measured levels of HCFC-123 in the aqueous stock solutions immediately after preparation ranged between 73 and 108% of their nominal values.

At all concentrations, test media were clear and colorless. Results of duplicate samples at the beginning of the test indicated that achieved HCFC-123 concentrations were lower than intended (between 54 and 76% of their nominal values), but measured levels increased during the test (to between 119 and 141% of the starting concentrations after 48 hours).

The lowest HCFC-123 concentration employed (mean measured value 2.24 mg/L) resulted in 5% immobilization and the highest (mean measured value 44.0 mg/L) caused 100% immobilization after 48 hours. The no-observed effect concentration was less than 2.24 mg/L (mean measured value).

The 24- and 48-hour EC_{50} of HCFC-123 for immobilization, calculated using mean measured concentrations, were 27.7 and 17.3 mg/L, respectively. The 24-hour values were approximations, obtained by nonlinear interpolation between nominal concentrations of 27.7 and 55.4 mg/L. The 48-hour EC_{50} value was calculated by the moving average method.

Reference: Life Sciences Research (1992). Unpublished Data, Report 91/0972.
Reliability: High because a scientifically defensible or guidelined method was used.

Additional Reference for Acute Toxicity to Invertebrates:

Data from this additional source supports the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont (1990). Unpublished Data, Haskell Laboratory Report No. 251-90 (also cited in TSCA Fiche OTS0530600 and OTS0539558).

4.3 Acute Toxicity to Aquatic Plants

Type: **96-hour EC_{50} for biomass and average specific growth**
Species: Green algae, *Selenastrum capricornutum*
Value: The 50% effect concentrations for biomass (E_bC_{50}) and average specific growth rate (E_rC_{50}) were 67.8 mg/L and 96.6 mg/L, respectively.
Method: The test was conducted in mineral salts medium at temperatures in the range 18.0 to 23.5ºC in an illuminated orbital incubator, using methods based on EPA TSCA Guideline 40 CFR 797.1060.

Triplicate algal cultures with a cell count of $1x10^4$/mL were exposed to HCFC-123 in sealed vessels containing mineral salts medium, at 5 nominal concentrations of 13.3, 42.5, 133, 425, and 1327 mg/L. Since the material was known to be volatile, it was injected through a rubber septum directly into the test medium. The cell density of each culture was measured, using a hemocytometer, at 24-hour intervals during the test. Growth rate (the rate of change in cell number with time) and biomass (the number of cells per mL) were both calculated. A set of control cultures was established in synthetic salts medium alone.

Five bottles were established for each test and control group. One bottle from each group, which was not incubated, was used for chemical analysis at the start of the test and then discarded. The remaining 4 bottles were incubated, of which 3 were used for cell counts during the test whilst the fourth was used for chemical analysis at 48 and 96 hours.

The minimum, maximum, and ambient temperature and light

intensity in the test area were determined each day. Following the removal of samples for chemical analysis at the start of the test, the temperature and pH of the contents of the fourth bottle in each group were determined. At the end of the test, after the removal of samples for analysis, the temperature and pH of the contents of each bottle were determined.

Exposure levels were monitored by a GC method of analysis. On 3 occasions during the test (0, 48, and 96 hours) duplicate samples were removed from the test medium at each concentration for analysis.

At the end of the test, in order to establish whether toxic levels of HCFC-123 caused inhibition of algal growth (were algistatic) or algal cell death (were algicidal), samples from cultures at the two highest nominal levels (1327 and 425 mg/L) were diluted (1:100) with fresh culture medium. These subcultures were incubated for 10 days and their cell densities were determined.

GLP: Yes

Test Substance: HCFC-123, purity not specified

Results: The temperature of the incubator ranged from 18.0-23.5ºC. The temperature of the contents of control and test bottles ranged, at the start of the test, from 22.2 to 22.3ºC and after 96 hours, from 19.2 to 21.9ºC. Their pH ranged between 7.2 and 7.9 at the start of the test. After 96 hours, values varied between 8.1 and 9.9 in control bottles and test bottles at 13.3, 42.5, 133, and 425 mg/L nominal, but ranged from 7.5 to 7.7 at 1327 mg/L nominal.

On the day of preparation, control and test cultures were clear and colorless. Measured concentrations of HCFC-123 were low compared to nominal values. At 13.3 and 42.5 mg/L, measured concentrations increased over the first 48 hours. During the second 48 hours of the test, all measured concentrations showed some decline. Measured HCFC-123 levels were maintained at 50 to 93% of initial (0 hours) levels across the range between the no-effect and maximum effect concentrations (nominally 133-1327 mg/L). These low aqueous levels were not unexpected because the volatility of HCFC-123 is likely to have caused its loss, both during dosing and subsequently from the test media into the headspace of the vessels. Furthermore, although HCFC-123 was soluble at the test concentrations, it was not easy to disperse under the conditions of the test. However, since

	toxic concentrations were achieved and maintained, it was considered that calculation of biological effect concentrations based on measured exposure levels was valid. Exposure at mean measured concentrations of 169 mg/L (nominally 1327 mg/L) resulted in a significant reduction in both biomass and average specific growth rate compared to control cultures. Biomass was also significantly reduced at 56.3 mg/L (nominally 425 mg/L). Thus the no-observed-effect concentration for biomass and growth rate, respectively, based on mean measured exposure concentrations, were 51.4 and 56.3 mg/L (nominal levels of 133 and 425 mg/L). Growth was reestablished in each subculture at the end of the test, indicating that at 1327 and 425 mg/L nominal, the material was algistatic.
Reference:	Life Sciences Research (1992). Unpublished Data, Report 91/0935.
Reliability:	High because a scientifically defensible or guidelined method was used.

Additional References for Acute Toxicity to Aquatic Plants: None Found.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type:	**Oral ALD**
Species/Strain:	Male rats/ChR-CD
Value:	9000 mg/kg
Method:	One young adult male rat per dose level was administered HCFC-123 as a solution in corn oil via intragastric intubation. Dose levels tested were 2250, 3400, 5000, 7500, 9000, 11,000, 13,934, and 15,024 mg/kg. Surviving animals were sacrificed after 14 days.
GLP:	No
Test Substance:	HCFC-123, purity 99%
Results:	Mortality occurred within 3 minutes at dose levels of 11,000, 13,934, and 15,024 mg/kg. Death occurred within 1 hour at 9000 mg/kg. Clinical signs observed at lethal doses included rapid respiration and prostration. Rapid, shallow respiration and belly-to-cage posture were observed on the day of dosing at 3400, 5000, and 7500 mg/kg. Wet perineal area on the day after dosing was observed at 5000 and 7500 mg/kg.
Reference:	DuPont Co. (1975). Unpublished Data, Haskell Laboratory

	Report No. 638-75 (also cited in TSCA Fiche OTS0000695 and OTS0530608).
Reliability:	High because a scientifically defensible or guidelined method was used.

Additional References for Acute Oral Toxicity: None Found.

Type:	**Inhalation 4-hour LC_{50}**
Species/Strain:	Male rats/Charles River – CD
Exposure Time:	4 hours
Value:	32,000 ppm
Method:	Six male rats/group were exposed to 20,700, 32,000, 33,700, 42,100, 52,500, or 55,000 ppm HCFC-123. The test material was vaporized, at room temperature, by bubbling air, at a regulated flow, through a gas washing bottle. The vaporized gas stream was diluted with an air stream, at a regulated flow, before entering the exposure chamber. The chamber atmospheres were analyzed by thermal conductivity gas chromatography. The oxygen content in the exposure chamber was ~19-20%. The initial body weights of the test animals ranged from 246 to 281 grams. Clinical signs were monitored during the test. No pathologic examinations were conducted.
GLP:	No
Test Substance:	HCFC-123, purity 99.86%
Results:	Mortality ratios of 0/6, 3/6, 3/6, 4/6, 6/6, and 6/6 were observed for the 20,700, 32,000, 33,700, 42,100, 52,500, and 55,000 ppm groups, respectively. At all concentrations, rats showed loss of mobility within 5 minutes after exposure. Other signs occurring within 5 minutes included lethargy, prostration, unresponsiveness to sound, and dyspnea. Rats that survived the exposure showed no noticeable clinical signs 30 minutes after the exposure had ended.
Reference:	DuPont Co. (1975). Unpublished Data, Haskell Laboratory Report No. 426-75 (also cited in TSCA Fiche OTS0000695, OTS0555755, and OTS0530610).
Reliability:	High because a scientifically defensible or guidelined method was used.

Additional References for Acute Inhalation Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Hazelton Laboratories, Inc. (1976). Project No. M165-162 (cited in TSCA Fiche

OTS0555786).

DuPont Co. (1966). Unpublished Data, Haskell Laboratory Report No. 16-66 (also cited in TSCA Fiche OTS0000695, OTS0571435, and OTS0530612).

DuPont Co. (1964). Unpublished Data, Haskell Laboratory Report No. 151-64 (also cited in TSCA Fiche OTS0000695, OTS0520325, OTS0555503, and OTS0530609).

Raventos, J. and P. G. Lemon (1965). Brit. J. Anesth., 37:716.

Burns, T. H. S. et al. (1962). Anaesthesia, 17(3):337-343 (CA58:7264h).

Marit, G. B. et al. (1994). Toxicol. Pathol., 22(4):404-414.

Burns, T. H. S. et al. (1982). Anaesthesia, 37:278-284.

Allied Corporation (1981). Report No. MA-25-78-15 (cited in TSCA Fiche OTS0000695).

DuPont Co. (1976). Unpublished Data, Haskell Laboratory Report No. 941-76 (also cited in TSCA Fiche OTS0000695, OTS0530602, and OTS0571407).

Type:	**Dermal LD_{50}**
Species/Strain:	Male and female rats/Crl:CD®BR
Exposure Time:	24 hours
Value:	> 2000 mg/kg
Method:	Rats were approximately 8 weeks old and weighed between 182 and 260 grams. The test material was applied to the clipped, intact skin of 5 male and 5 female rats at a dosage of 2000 mg/kg. Sterile gauze pads were applied to the treated site and the rats were then wrapped with successive layers of plastic film, gauze bandage, and elastic adhesive bandage. Approximately 24 hours after treatment, the wrappings were removed. Excess test material was washed from the animals' back with water and the animals were weighed and observed for clinical signs of toxicity. Observations for clinical signs were made approximately 3 hours after dosing and then daily thereafter for 14 days (weekends excluded). The animals were periodically weighed during this 14-day period. At the end of the test period, the rats were subjected to a gross pathological examination.
GLP:	Yes
Test Substance:	HCFC-123, purity approximately 99.98%
Results:	No rats died within 14 days after dosing. The only clinical signs of toxicity observed were red nasal or ocular discharge

	in 1 male and 1 female rat. No dermal irritation was observed. Slight to moderate body weight losses (up to 12% of initial body weight) were observed 1 day after treatment. No gross pathological abnormalities were observed in the treated rats.
Reference:	DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 577-88 (also cited in TSCA Fiche OTS0000695 and OTS0530598).
Reliability:	High because a scientifically defensible or guidelined method was used.

Type:	**Dermal LD_{50}**
Species/Strain:	Male and female rabbits/New Zealand White
Exposure Time:	24 hours
Value:	> 2000 mg/kg
Method:	Rabbits, weighing between 1972 and 2169 grams, were fitted with plastic collars to prevent ingestion of the test material or disruption of the wrappings. The test material was applied to the clipped, intact skin of 5 male and 5 female rabbits at a dosage of 2000 mg/kg. Sterile gauze pads were applied to the treated site and the rabbits were then wrapped with successive layers of plastic film, gauze bandage, and elastic adhesive bandage. Approximately 24 hours after treatment, the wrappings were removed. Excess test material was washed from the animals' back with water, and the animals were weighed and observed for clinical signs of toxicity. Observations for clinical signs were made approximately 24 hours after dosing and daily thereafter for 14 days (weekends excluded). The animals were periodically weighed during this 14-day period. At the end of the test period, the rabbits were subjected to a gross pathological examination.
GLP:	Yes
Test Substance:	HCFC-123, purity approximately 99.98%
Results:	No rabbits died within the 14-day observation period. Slight to moderate erythema was seen in 6/10 rabbits by one day after treatment. By day 5, no dermal irritation was seen. Slight body-weight losses (up to 2% of initial body weight) were observed 1 day post-treatment. No gross pathological abnormalities were seen in any treated rabbit.
Reference:	DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 578-88 (also cited in TSCA Fiche OTS0000695 and OTS0530597).
Reliability:	High because a scientifically defensible or guidelined method was used.

Additional References for Acute Dermal Toxicity: None Found.

Type:	**Dermal Irritation**
Species/Strain:	Male and female rabbits/New Zealand White
Method:	HCFC-123 was evaluated for acute skin irritation potential in 4 male and 2 female rabbits. Rabbits weighed between 2316 and 2617 grams. Each rabbit was placed into a stock which was fitted with a piece of rubber sheeting. The rabbits remained in the stock throughout the exposure period and during that time did not have access to food or water. A 0.5 mL aliquot of HCFC-123 was applied directly to each site beneath a gauze square that was held in place with tape. In addition, sodium lauryl sulfate was used as a positive control and was tested concurrently with HCFC-123. A 0.5 gram aliquot of sodium lauryl sulfate, moistened with distilled water, was applied to a separate test site on the same animal. The test site was covered with a gauze square that was held in place with tape. The rubber sheeting was then wrapped around the animal and secured with clips to retard evaporation and to keep the materials in contact with the skin without undue pressure. Approximately 4 hours after application of the test material, the gauze squares were removed and the test sites were washed with water and gently wiped dry. The test sites were evaluated for erythema, edema, and other evidence of dermal effects and were scored according to the Draize scale. Additional evaluations were made at approximately 24, 48, and 72 hours after removal of the patches. For the positive control material, dermal evaluations were also made daily (excluding weekends) until study termination (test day 15). The adjacent areas of untreated skin were used for comparison.
GLP:	Yes
Test Substance:	HCFC-123, purity approximately 99.98%
Results:	HCFC-123 produced no dermal irritation in any treated rabbit. Sodium lauryl sulfate (the positive control material) produced mild or moderate erythema with slight to moderate edema by 4 hours after treatment. By 48 hours, severe erythema with slight or mild edema was observed. Other dermal effects of the positive control included necrosis, superficial necrosis, thickening, raw area or fissuring of the skin, eschar, and epidermal scaling. Severe erythema and some dermal effects of the positive control were still evident at study termination.
Reference:	DuPont Co. (1988). Unpublished Data, Haskell Laboratory

Report No. 535-88 (also cited in TSCA Fiche OTS0000695).

Reliability: High because a scientifically defensible or guidelined method was used.

Additional References for Dermal Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1975). Unpublished Data, Haskell Laboratory Report No. 678-75 (also cited in TSCA Fiche OTS0000695 and OTS0530606).

DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 577-88 (also cited in TSCA Fiche OTS0000695 and OTS0530598).

DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 578-88 (also cited in TSCA Fiche OTS0000695 and OTS0530597).

Type:	**Primary Dermal Irritation and Sensitization**
Species/Strain:	Male guinea pigs/Albino
Method:	The test for primary irritation was conducted by applying, and lightly rubbing in 1 drop (~0.05 mL) each of a 50% and a 10% solution (wt/vol) of the test material in propylene glycol on the shaved intact shoulder skin of 10 male guinea pigs. To test for the sensitization potential, a series of 4 sacral intradermal injections was given, one each week over a 3-week period, which consisted of 0.1 mL of a 1% solution (vol/vol) of test material in dimethyl phthalate (DMP). Following a 2-week rest period, the test animals were challenged for sensitization by applying and lightly rubbing in 1 drop (~0.05 mL) each of a 50% and a 10% solution (wt/vol) of test material in propylene glycol on the shaved intact shoulder skin. A group of 10 previously unexposed guinea pigs received similar applications at the time of challenge to provide a direct comparison of the challenge reactions on skin of similar age.
GLP:	No
Test Substance:	HCFC-123, purity approximately 99.9%
Results:	HCFC-123 produced no irritation or sensitization when tested on shaved, intact skin of male albino guinea pigs using a 50% and a 10% solution in propylene glycol.
Reference:	DuPont Co. (1975). Unpublished Data, Haskell Laboratory Report No. 678-75 (also cited in TSCA Fiche OTS0000695 and OTS0530606).

Reliability: High because a scientifically defensible or guidelined method was used.

Additional References for Dermal Sensitization: None Found.

Type:	**Eye Irritation**
Species/Strain:	Rabbit/Albino
Method:	The test material was placed in the right conjunctival sac of 2 rabbits. Three groups were tested: Group 1 received 0.1 mL of HCFC-123 undiluted; Group 2 received 0.2 mL of a 50:50 mixture of HCFC-123 and propylene glycol; and Group 3 received 0.1 mL of propylene glycol. Because of the low boiling point of HCFC-123, the authors were concerned that irritation might be caused merely by the cooling effect of the rapid evaporation. For this reason a 50:50 mixture in propylene glycol (a high boiling solvent) was also tested. In all groups, after 20 seconds, one treated eye was washed with tap water for 1 minute. The treated eye of the other rabbit was not washed. Observations of the cornea, iris, and conjunctiva were made with a hand-slit lamp at 1 and 4 hours, and at 1, 2, 3, 7, and 14 days. Fluorescein stain and a biomicroscope were used at examinations after the day of treatment.
GLP:	No
Test Substance:	HCFC-123, purity 99%
Results:	HCFC-123 produced mild to moderate conjunctival irritation with no corneal or iritic involvement in an unwashed eye. The eye dosed with the HCFC-123 and promptly washed had mild to slight transient corneal opacity and mild to moderate conjunctival irritation with no iritic involvement. Both eyes were normal within 3-7 days. Eyes dosed with the 50:50 mixture had slight to moderate corneal opacity with partial circumcorneal vascularization, mild iritic congestion, and mild to severe conjunctival irritation. The washed eye had slight to moderate corneal opacity, slight iritic congestion, and mild to moderate conjunctival irritation. Both eyes were normal within 14 days. Eyes dosed with propylene glycol produced mild to moderate conjunctival irritation. Both eyes were normal within 3 days. The eyes dosed with the 50:50 mixture were much more irritated than those dosed with the neat material. The reason

	was probably because the mixture allowed HCFC-123 to be in intimate contact with the eye longer than the neat HCFC-123 which boiled out.
Reference:	DuPont Co. (1975). Unpublished Data, Haskell Laboratory Report No. 747-75 (also cited in TSCA Fiche OTS0539607 and OTS0000695).
Reliability:	High because a scientifically defensible or guidelined method was used.

Additional References for Eye Irritation: None Found.

Type:	**Cardiac Sensitization**
Species/Strain:	Male dogs/Beagle
Value:	EC_{50} = 19,500 ppm (95% confidence limits, 13,000-28,000 ppm).
Method:	Male beagle dogs were exposed to various concentrations of HCFC-123. The test animal received an intravenous control injection of adrenalin (0.008 mg/kg) prior to exposure and a challenge injection (same dosage) after breathing the test substance for 5 minutes. An electrocardiogram was recorded during each experimental run and a "marked response" was noted when an arrhythmia developed which was considered to pose a serious threat to life (multiple consecutive ventricular beats or bigeminal rhythm) or which ended in cardiac arrest (ventricular fibrillation). Each dog was tested one at a time, in such a way that the results of any test was known before the next was begun. Each test was run at a concentration level different from the preceding one. Therefore, the staircase method (Finney, 1964) was the method of choice to estimate an EC_{50} for cardiac sensitization. With this statistical procedure, a series of concentrations was chosen, e.g. … X_{-2}, X_{-1}, X_0, X_1, X_2 …, where X_0 was the estimated EC_{50} and the values of X were equally spaced. The result of any one test determined the concentration level for the next test: if a dog exhibited a "marked response," the next dog was tested at a concentration one step lower, if the animal showed no "marked response," the next dog was tested at a level one step higher. The first test was run at X_0. Using this method, a concentration of 4.0% (40,000 ppm) was chosen as the estimated X_0 and concentrations selected below and above that level included 0.5 (5000 ppm), 1.0 (10,000 ppm), 2.0 (20,000 ppm), and 8.0% (80,000 ppm). A total of 12 individual dogs were used for this study.

	HCFC-123, a liquid at room temperature, was generated from a syringe drive into a heated, metered airstream. The compound-air mixture then passed into a heated 1-L mixing flask and subsequently to the dog mask. Exposure concentration was analyzed by gas chromatography.
GLP:	No
Test Substance:	HCFC-123, purity not specified
Results:	Seven of 12 dogs exposed to HCFC-123 exhibited a "marked response", 6 of which resulted in ventricular fibrillation and death. Three of the 12 tested dogs were exposed to 10,000 ppm and showed no reaction, 6 of the 12 dogs were exposed to 20,000 ppm and 4 of these 6 showed marked responses; all 3 dogs exposed to 40,000 ppm showed marked responses. In the 6 dogs that died, CNS depression (decreased motor reflexes and lassitude) and tachycardia were observed prior to the challenge injection of adrenalin. In the dog that survived the 40,000 ppm dose and exhibited a "marked response," CNS excitation (struggling, tachycardia, and labored breathing) preceded the challenge injection of adrenalin. Signs of CNS depression were also observed in the dogs that showed no positive responses.
Reference:	DuPont Co. (1973). Unpublished Data, Haskell Laboratory Report No. 132-73 (also cited in TSCA Fiche OTS0000695, OTS0530603, and OTS0571234). Finney, D. J. (1964). Probit Analysis, 2nd ed., pp. 226-232, Cambridge University Press, New York.
Reliability:	Medium because a suboptimal study design was used where animals were not individually titrated with adrenalin.

Additional References for Cardiac Sensitization: None Found.

5.2 Repeated Dose Toxicity

Type:	**2-Year Inhalation Study**
Species/Strain:	Rats/Crl:CD®BR
Sex/Number:	Males and females/80 per sex per group
Exposure Period:	2 years
Frequency of Treatment:	6 hours/day, 5 days/week (weekends and holidays excluded)
Exposure Levels:	0, 300, 1000, 5000 ppm
Method:	Groups of 80 male and 80 female rats were exposed to 0, 300, 1000, or 5000 ppm HCFC-123 for approximately 104 weeks. Food and water were available *ad libitum* except during exposures. The rats were approximately 41 days of

age at study start.

Rats were exposed whole-body to the test substance. During exposures, chamber temperature, humidity of the chamber air, and airflow rates were monitored. Four dedicated chambers (4 m^3) constructed of stainless steel and glass were used for the testing. The chambers were operated in a one-pass, flow-through mode with air flow rates adequate to provide sufficient oxygen for test animals, to prevent contamination from volatiles derived from animal excreta, and to enable adequate distribution of HCFC-123 in the chambers. HCFC-123 vapor was generated by evaporating the liquid test material in a stream of metered air. The vapor was diluted with filtered air to the desired concentrations for each of the test chambers. Filtered air alone was metered in an identical manner into the control chamber. Chamber atmospheres were quantitatively analyzed for HCFC-123 by gas chromatography.

Rats were weighed weekly for the first 3 months of the study and every 2 weeks thereafter. Food consumption and clinical signs of toxicity were monitored throughout the study. Cage-site examinations to detect moribund or dead rats and abnormal behavior and appearance were conducted at least once daily throughout the study. Ophthalmoscopic examinations were conducted prior to study start, and approximately 12 and 24 months after study initiation. Evaluations for hematology, clinical chemistry, and urinalysis parameters were performed approximately 6, 12, 18, and 24 months after study initiation. Nine hematology and 20 clinical chemistry parameters were measured or calculated. On the day prior to the blood collection, an overnight urine specimen was collected, and 13 urine chemistry parameters were measured or calculated. Approximately 12 months after study initiation, 10 rats per sex per group were sacrificed, selected organs weighed (9 in total), and tissues were examined for gross and microscopic lesions. All surviving rats underwent necropsy at 24 months after study initiation. Selected organs were weighed (9 in total) and tissues were examined for gross and microscopic lesions. Approximately 50 organs and/or tissues were saved for microscopic examinations. The first 5 rats from each group designated for the 12-month sacrifice were also evaluated for cell proliferation.

GLP: Yes

Test Substance: HCFC-123, purity ≥99.8%

Results:

The overall mean concentrations of HCFC-123 in the exposure chambers for the 2-year test period were 0, 300, 1002, and 4997 ppm, corresponding to the nominal concentrations of 0, 300, 1000, and 5000 ppm, respectively. The difference in concentration measured between the center of the chamber and the bottom of the chambers for each of the test chambers was approximately 6%, indicating good distribution of HCFC-123 within the chambers.

Mean values for temperature and relative humidity were similar between the 4 chambers. In general, chamber temperatures ranged between 17-25ºC. On several occasions, the chamber temperature reached 29ºC. The elevated chamber temperature did not appear to have an effect on the animals as indicated by body weight or incidence of clinical observations. Mean airflow for all 4 chambers was similar.

All rats exposed to 5000 ppm and females exposed to 1000 ppm had lower body weight and body weight gain. Females exposed to 300 ppm also had lower body weight over a period of several months. Food consumption was slightly higher and food efficiency slightly lower in males and females exposed to 5000 ppm. During exposures, rats exposed to 5000 ppm were less responsive to auditory stimuli compared to controls. However, by the time residual test material had exhausted from the chamber and the rats returned to the animal room, the responsiveness of rats exposed to 5000 ppm was similar to control. Males and females exposed to 1000 or 5000 ppm had higher incidences of 1 or more grossly observed clinical observations which included stained fur, wet perineum, and wet inguen. In addition, 5000 ppm females had a decreased incidence of colored discharge from the eye, and 1000 and 5000 ppm females had a decreased incidence of skin sores. Males at 5000 ppm had a significantly higher incidence of grossly observed inguinal masses; however, females at 1000 and 5000 ppm had a significantly lower incidence of inguinal masses and total masses.

Greater survival was noted for both males and females at 1000 and 5000 ppm. The increased survival was correlated with a decreased incidence of spontaneous lesions in aged rats.

Serum triglyceride concentrations were significantly

decreased at all exposure concentrations for both sexes compared to controls. Serum glucose concentrations were significantly decreased at all exposure concentrations at the 6- and 12-month evaluations. However, at the 18-month evaluation, only 1000 and 5000 ppm males and 5000 ppm females had lower glucose concentrations. By the 24-month evaluation, glucose concentrations were similar to control at all exposure concentrations. Serum cholesterol was also lower in all treated females and in males in the 5000 ppm group. Serum albumin was significantly higher in males in the 1000 and 5000 ppm groups, and serum globulin was significantly lower in the 1000 and 5000 ppm males and in all treated females. Urinary fluoride was generally higher in all treated animals. Urine volume was higher and urine osmolality lower in all treated males at the 6- and 12-month evaluations.

Ophthalmologic evaluations did not reveal any grossly observable abnormalities at any time point evaluated. However, histological evaluation of the retina indicated a significantly increased incidence of diffuse retinal atrophy in both males and females at all concentration levels (See incidence table below).

At the 12-month sacrifice, a compound-related increase in mean relative liver weight was observed for 5000 ppm males and females; however, no compound-related gross or microscopic morphological changes were seen.

At the 24-month sacrifice, 5000 ppm males had increased mean relative liver weights. In addition, there were compound-related increases in the incidences of grossly observed large and discolored livers in 5000 ppm males and in liver masses in 5000 ppm females. Mean absolute kidney weights were lower in 5000 ppm males and in 1000 and 5000 ppm females. The decrease in kidney weights was attributed to the reduction in the incidence and severity of spontaneously occurring glomerulonephropathy.

At the 24-month sacrifice, the incidence of benign hepatocellular adenomas in the 5000 ppm males and in all test groups of females was increased. The incidence of basophilic cellular alteration in the liver was increased in all test groups of male and females. The incidence of hepatic cholangiofibroma was also increased in the 5000 ppm females. Males exposed to 5000 ppm also had a compound-

related increased incidence of hepatic focal necrosis. The incidence of hepatic centrilobular fatty change was also increased in the 5000 ppm males and females. Females exposed to 5000 ppm had an increased incidence of sinusoidal ectasia. In addition, 1000 and 5000 ppm males and 5000 ppm females had an increased incidence of hepatic cystic degeneration.

The incidence of benign pancreatic acinar cell adenomas was increased in all male test groups. Pancreatic acinar cell hyperplasia was also increased in the 1000 and 5000 ppm males and females. Since pancreatic acinar cell adenomas are a continuum of acinar cell hyperplasia, the incidence of acinar cell adenomas and hyperplasia in all test groups of females is also considered to be compound-related.

The incidence of benign testicular interstitial adenomas and focal interstitial cell hyperplasia in the testes was also increased in all male test groups. In addition, 5000 ppm males had an increased incidence of unilateral tubular atrophy which was the result of tumor induced pressure atrophy. Bilateral tubular atrophy was significantly decreased in 5000 ppm males, and testicular polyarteritis was decreased in all test groups.

Diffuse retinal atrophy was increased in all test groups of males and females, and was considered an indirect compound-related effect. This lesion is spontaneous in aged rats, and may be modulated by light, sex, pituitary and ovarian hormones, and decreased levels of retinal taurine.

Males exposed to 5000 ppm had an increased incidence of focal degeneration of the adrenal cortex; however, it was minimal to mild in severity and was considered to be a compound-related effect of minimal or no biological significance. In the 5000 ppm females, the incidence of ovarian cysts was significantly increased; however, since they were minimal to mild in severity these cysts were considered to be of minimal or no biological significance.

Decreased incidence of several spontaneous lesions was observed and was attributable to the beneficial effects of reduced body weight and/or lower serum lipid levels.

The incidences of tumors (discussed above) in male rats can be found in the following table.

Tumor Type	0 ppm	300 ppm	1000 ppm	5000 ppm
Hepatocellular adenoma – singular	3/67 (4%)	2/66 (3%)	2/66 (3%)	5/66 (8%)
Hepatocellular adenoma – multiple	0/67 (0%)	0/66 (0%)	0/66 (0%)	3/66 (5%)
Hepatocellular adenoma – total	3/67 (4%)	2/66 (3%)	2/66 (3%)	8/66 (12%)
Basophilic cellular alteration in the liver	8/67 (12%)	10/66 (15%)	20/66 (30%)	30/66 (45%)
Hepatic focal necrosis	0/67 (0%)	4/66 (6%)	4/66 (6%)	7/66 (11%)
Hepatic centrilobular fatty change	1/67 (1%)	2/66 (3%)	1/66 (2%)	28/66 (42%)
Hepatic cystic degeneration	22/67 (33%)	28/66 (42%)	32/66 (48%)	33/66 (50%)
Pancreatic acinar cell adenoma	1/67 (1%)	4/66 (6%)	12/64 (19%)	14/66 (12%)
Pancreatic acinar cell hyperplasia	5/67 (7%)	6/66 (9%)	13/64 (25%)	19/66 (29%)
Diffuse retinal atrophy	15/61 (25%)	23/57 (40%)	34/62 (55%)	38/60 (63%)
Testicular interstitial cell adenoma – bilateral	1/67 (1%)	6/66 (9%)	5/66 (8%)	6/66 (9%)
Testicular interstitial cell adenoma – unilateral	3/67 (4%)	6/66 (9%)	4/66 (6%)	8/66 (12%)
Testicular interstitial cell adenoma – total	4/67 (6%)	12/66 (18%)	9/66 (14%)	14/66 (21%)

Testicular focal interstitial hyperplasia	8/67 (12%)	15/66 (23%)	23/66 (35%)	30/66 (45%)
Testicular unilateral tubular atrophy	5/67 (7%)	9/66 (14%)	9/66 (14%)	15/66 (23%)
Testicular bilateral tubular atrophy	16/67 (24%)	14/66 (21%)	11/66 (17%)	7/66 (11%)
Testicular polyarteritis	17/67 (25%)	1/66 (2%)	1/66 (2%)	0/66 (0%)
Focal degeneration of adrenal cortex	16/67 (24%)	4/66 (6%)	6/66 (9%)	27/66 (41%)

The incidences of tumors (discussed above) in female rats can be found in the following table.

Tumor Type	0 ppm	300 ppm	1000 ppm	5000 ppm
Hepatocellular adenoma – singular	0/65 (0%)	5/67 (8%)	2/67 (3%)	6/69 (9%)
Hepatocellular adenoma – multiple	0/65 (0%)	0/67 (0%)	0/67 (0%)	1/69 (1%)
Hepatocellular adenoma – total	0/65 (0%)	5/67 (8%)	2/67 (3%)	7/69 (10%)
Hepatic cholangiofibroma – singular	0/65 (0%)	0/67 (0%)	0/67 (0%)	5/69 (7%)
Hepatic cholangiofibroma – multiple	0/65 (0%)	0/67 (0%)	0/67 (0%)	1/69 (1%)
Hepatic cholangiofibroma – total	0/65 (0%)	0/67 (0%)	0/67 (0%)	6/69 (9%)
Hepatic centrilobular fatty change	2/65 (3%)	0/67 (0%)	4/67 (6%)	20/69 (29%)

Hepatic sinusoidal ectasia	8/65 (12%)	15/67 (22%)	15/67 (22%)	25/69 (36%)
Hepatic cystic degeneration	1/65 (2%)	3/67 (4%)	6/67 (9%)	7/69 (10%)
Basophilic cellular alteration in the liver	17/65 (26%)	26/67 (39%)	32/67 (48%)	46/69 (67%)
Pancreatic acinar cell adenoma	0/65 (0%)	2/66 (3%)	0/67 (0%)	2/69 (3%)
Pancreatic acinar cell hyperplasia	0/65 (0%)	4/66 (6%)	6/67 (9%)	8/69 (12%)
Diffuse retinal atrophy	15/65 (23%)	35/67 (52%)	55/67 (82%)	44/69 (64%)
Ovarian cysts	16/65 (25%)	21/67 (31%)	26/67 (39%)	32/69 (46%)

All treated males and females exposed to 1000 or 5000 ppm of HCFC-123 had higher hepatic β-oxidation activity compared to controls, indicating an induction of hepatic peroxisome proliferation. Compound-related differences in the rate of hepatic cell proliferation were not seen at any exposure level at the 12-month sacrifice. This indicates that HCFC-123 did not induce an increase in regenerative repair of the liver.

A no-observable effect level was not achieved for this study based on effects in clinical chemistry parameters at all concentrations, lower body weight and body weight gain at 300, 1000, and 5000 ppm; higher liver weights at 5000 ppm; and increased incidence of neoplastic and non-neoplastic morphological changes and higher hepatic peroxisomal β-oxidation activity at all concentrations.

Reference: DuPont Co. (1991). Unpublished Data, Haskell Laboratory Report No. 669-91 (also cited in TSCA Fiche OTS0528777, OTS0000695-11, OTS0530498, OTS0530498-1, OTS0543416, and OTS0530498-3).

Malley, L. A. et al. (1995). Fund. Appl. Toxicol., 25(1):101-114.

Reliability: High because a scientifically defensible or guidelined

method was used.

Additional References for Repeated Dose Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1995). Unpublished Data, Haskell Laboratory Report No. 57-95.

Keller, D. A. et al. (1998). Drug Chem. Toxicol., 21(4):405-411.

DuPont Co. (1976). Unpublished Data, Haskell Laboratory Report No. 149-76 (also cited in TSCA Fiche OTS0000695, OTS0530610, OTS0571361, OTS520869, and OTS0571675).

Hoechst (1995). Unpublished Data, Report No. 95.0347.

Hoechst AG (1996). Unpublished Data, Report 7/95, Hoechst Study No. 95.0069.

DuPont Co. (1997). Unpublished Data, Haskell Laboratory Report HL-1997-00152.

DuPont Co. (1989). Unpublished Data, Haskell Laboratory Report No. 229-89 (also cited in TSCA Fiche OTS0000695-3, OTS0555224, and OTS0530616, and in Rusch, G. M. et al. (1994). Fund. Appl. Toxicol., 23:169-173).

ICI (1990). Unpublished Data, Report CTL/P/2706 (cited in TSCA Fiche OTS0000695-11).

DuPont Co. (1992). Unpublished Data, Haskell Laboratory Report No. 828-92 (also cited in TSCA Fiche OTS0530498-4 and OTS0530498-2).

DuPont Co. (1989). Unpublished Data, Haskell Laboratory Report No. 594-89 (also cited in TSCA Fiche OTS0000695-7 and OTS0530615, and in Rusch, G. M. et al. (1994). Fund. Appl. Toxicol., 23:169-173).

Allied Chemical (1977). Unpublished Data, Industrial Bio-Test Laboratory Report, IBT No. 8562-09344.

DuPont Co. (1978). Unpublished Data, Haskell Laboratory Report No. 229-78 (also cited in TSCA Fiche OTS0000695, OTS0530613, OTS0546291, OTS555534, and OTS0556332).

Allied Signal (1994). Unpublished Data, Huntingdon Research Report ALS

3/931038.

5.3 Developmental Toxicity

Study No. 1	
Species/Strain:	Rabbits/New Zealand White
Sex/Number:	Female/24 per group
Route of Administration:	Whole-body inhalation
Exposure Period:	Days 6 through 18 of gestation
Frequency of Treatment:	6 hours/day
Exposure Levels:	0, 500, 1500, 5000 ppm
Method:	Female rabbits were 4 to 5 months old at receipt and weighed between 2967 and 4123 g. Food and water were available *ad libitum* except during exposures. Rabbits were housed individually except during mating. A 12 hour light/dark cycle was controlled via an automatic timer. Temperature and relative humidity were monitored throughout the study. Rabbits were naturally mated. Each female was placed into the male rabbits' cage. When coitus was observed, the female was removed and returned to her original cage. Following an interval of 1 to 2 hours, the female was placed into the cage of a second, different male. When coitus was observed with the second male, the female was considered mated and returned to her cage. The day on which evidence of mating was observed with both males was defined as day 0 of gestation. Rabbits were exposed via whole-body inhalation for 6 hours/day during days 6 through 18 of gestation. Exposure levels evaluated were 500, 1500, and 5000 ppm. A chamber-exposed sham-air treated control group of comparable size was also tested. Animals were exposed in Wahmann glass and stainless steel exposure chambers which had a total volume of 6 m^3. HCFC-123 was vaporized using heated nitrogen in a counter-current volatization chamber. The HCFC-123 was delivered by a metered pump, via tubing, to the coiled glass rod in the volatization chamber. Samples for determination of HCFC-123 exposure levels were performed using gas chromatography. Chamber temperature, relative humidity, and air flow were also monitored in the exposure chamber.

In-life observations included periodic measurements of body weight, food consumption, and clinical findings. Animals were sacrificed on day 30 of gestation and given a gross postmortem evaluation. Corpora lutea were counted and the uteri evaluated for the number of implantation sites and the number of live, dead, and resorbed fetuses. Fetuses were weighed, evaluated for external irregularities, and processed for soft tissue and skeletal evaluations.

GLP: Yes

Test Substance: HCFC-123, purity ≥ 99.8%

Results: The mean daily analytical concentrations were 502, 1469, and 4828 ppm for the 500, 1500, and 5000 ppm groups, respectively. Chamber distribution analyses indicated that there was no significant gradient within each exposure chamber.

The mean chamber temperature was 21±2, 22±2, 21±2, and 21±2ºC for the 0, 500, 1500, and 5000 ppm groups, respectively. Mean chamber relative humidity was 42±11, 34±12, 45±9, and 34±10% for the 0, 500, 1500, and 5000 ppm groups, respectively. Although chamber temperature and relative humidity deviated from the specified ranges on occasion, these levels were considered acceptable.

No mortality occurred in the 0, 500, or 1500 ppm groups. The low mortality rate (4.2%, 1/24 females) seen at 5000 ppm was not considered to represent a treatment-related response.

Maternal toxicity was evident at all exposure levels evaluated (500, 1500, and 5000 ppm). Over the entire day 6-18 exposure interval of gestation, a mean weight loss was seen in each of the treated groups in comparison to a slight mean weight gain seen in the concurrent control group. A clear exposure relationship was evident and differences from control were statistically significant. Mean daily food consumption values for the exposure groups during the day 6-18 gestation interval were lower than control data, and statistically significant differences were seen for the following intervals: 500 ppm (days 8-10 and 13), 1500 ppm (days 6-14 and 16) and 5000 ppm (days 6-13 and 16). No other maternal toxicity was seen among the exposure groups.

No embryotoxic, fetotoxic, or teratogenic effects were seen

at the exposure levels evaluated.

Pregnancy rates for the 0, 500, 1500, and 5000 ppm groups were 87.5% (21/24), 95.8% (23/24), 91.7% (22/24), and 87.5% (21/24), respectively. No evidence of aborted fetuses was seen among the 0, 500, or 5000 ppm groups. In the 1500 group, two females aborted. In the absence of aborted females at the highest concentration level, the low incidence of aborted fetuses in the mid-exposure level was not considered indicative of a direct treatment-related response.

A summary of reproductive outcomes (means/litter unless otherwise noted) is provided in the table below:

Concentration (ppm):	0	500	1500	5000
Corpora lutea:	10.0	10.4	9.1	9.3
Implantations:	9.4	9.3	7.8	8.9
No. of Resorptions:	0.2	0.7	0.4	0.6
Total No. of Fetuses:	9.1	8.6	7.4	8.3
Total No. of Live Fetuses:	9.1	8.6	7.4	8.3
Mean Fetal Weight (g):	47.72	49.06	49.47	44.68
Sex Ratio (total males/total females):	0.9	1.0	1.2	1.0

The number of corpora lutea per pregnant female was comparable between the control and each treated group. The mean number of uterine implantations per pregnant female were comparable between the control, 500, and 5000 ppm groups. In the 1500 ppm group, a slight, albeit statistically significant reduction in the mean number of uterine implants was seen. This incidence, while lower than concurrent control data, was within the range of historical control data for the laboratory and in absence of a similar reduction in the high-dose group, this response was not considered indicative of a treatment-related effect. Historical control data for implantations (for 17 studies conducted between 1982-1987) was 8.8 (range of 7.5 – 10.5).

The incidence of females with resorptions among their *in utero* litters was slightly higher than control in each of the treated groups; however, these differences were not statistically significant.

The mean number of live fetuses per pregnant female was comparable between the control, 500, and 5000 ppm groups. This incidence in the 1500 ppm group was slightly lower than control and this difference was statistically significant. The mean number of live fetuses in the 1500 ppm group was within the range recent control historical control data. In absence of a similar reduction in mean number of live fetuses at the high-dose level, the slight, albeit statistically significant reduction in this parameter at 1500 ppm was not considered indicative of a treatment-related response. Historical control data for number of live fetuses (for 17 studies conducted between 1982-1987) was 8.0 (range of 6.3–8.9). No dead fetuses were recovered *in utero* for control or treated females.

Mean fetal weights as a composite for both sexes and distinguished by sex, were considered comparable between the control, 500, and 1500 ppm groups. In the 5000 ppm group, mean fetal weights were slightly lower than control (-6.4% for composite fetal weight data, -6.9% for male fetuses, and –5.5% for female fetuses); however, these differences were not statistically significant. Mean fetal weight data for the 5000 ppm group were within the range of recent historical control data (1982-1987) for the laboratory. Therefore, the slight decrease in mean fetal weight seen at 5000 ppm was not considered indicative of a treatment-related effect. Historical control data for mean male fetal weights was 46.7 g (range of 40.0 – 50.4 g). Historical control data for mean female fetal weights was 45.5 g (range of 39.6 – 48.1 g). Historical control data for mean composite fetal weight was 46.3 g (range of 40.5 – 49.6 g).

The mean number of male and female fetuses per litter was considered comparable between the control and treated groups. Likewise, the ratio of male/female fetuses was similar between these same groups.

No compound-related statistically significant external, visceral, or skeletal variations or malformations were observed in the fetal examinations.

	The NOEL for developmental toxicity was 5000 ppm.
Reference:	Bio/dynamics (1989). Project No. 88-3304 (also cited in TSCA Fiche OTS0000695-3, Schroeder, R. E. et al. (1995). Teratology, 51(3):196, and Malinverno, G. et al. (1996). Fundam. Appl. Toxicol., 34(2):276-287). Khera, K. S. (1985). Teratology, 31:129-153.
Reliability:	High because a scientifically defensible or guidelined method was used.

Study No. 2

Species/Strain:	Rats/Charles Rivers-CD Albino
Sex/Number:	Female/25 per group
Route of Administration:	Inhalation
Exposure Period:	Days 6 through 15 of gestation
Frequency of Treatment:	6 hours/day
Exposure Levels:	0, 1% (10,000 ppm)
Method:	Female rats were bred at Charles River Breeding Laboratories. Pregnancy was confirmed by finding sperm in the vaginal smear of females caged overnight with males. That morning was counted as day 1 of gestation. The animals were shipped directly to Haskell Laboratory the following day. Rats were housed individually. Food and water were available 1 hour after the exposure until the next day. On day 6 through 15 of gestation, groups of 25 rats were exposed in 1.4 m^3 stainless steel chambers to 1% HCFC-123. The control group was exposed to air in a similar chamber. Vapors from heated cylinders of HCFC-123 were added at measured rates to the air supply leading to the exposure chambers. The concentration of test material was monitored using gas chromatographic methods. The animals were observed daily and weighed twice weekly and on the day of laparotomy. Food consumption was not measured. Prior to sacrifice, the females were anesthetized. The uterus was removed and weighed. The uterine horns were opened and the fetuses removed. The following observations and enumerations were made: number of corpora lutea, number of implantation sites, number and location of live and dead fetuses, number and location of late and early resorptions, weight and crown-rump length of live

fetuses, and gross examination of all fetuses for external anomalies. About one-half of the fetuses from each litter were examined for detection of skeletal abnormalities. The remaining fetuses were examined for visceral and neural anomalies.

GLP: No

Test Substance: HCFC-123, purity 99.9509%

Results: The average analytically-determined concentration during the 10-day exposure period was 0.94±0.07%.

Body weight gain patterns of females during and after exposure to HCFC-123 were not different from controls. Animals showed a lack of coordination during the early phase of daily exposure followed by reduced activity and responsiveness to noise.

All parameters measuring reproductive capacity were comparable with the control group. A summary of reproductive outcomes (means/litter unless otherwise noted) is provided in the table below:

Concentration (ppm):	0	10,000
Corpora lutea:	12.7	12.6
Implantations:	10.1	10.6
No. of Resorptions:	9	7
Total No. of Fetuses:	9.6	10.1
Total No. of Live Fetuses:	9.6	10.1
Mean Fetal Weight (g):	3.92	4.13
Sex Ratio:	NR	NR

NR= Fetal sex was not recorded; therefore, sex ratios could not be calculated.

No gross changes or abnormalities were observed in the

uterine horns and ovaries. No gross pathological changes were detected in tissues and organs. Except for hydrocephaly found in one fetus in the control group, no other major malformations were detected. The minor anomalies and common variants observed were biological and were related to chronological age of the fetuses (delayed ossification of sternebrae and thoracic centra), genetic background (14^{th} rudimentary and wavy ribs, hydronephrosis, runts), and possible physical factors at laparotomy (subcutaneous hematomas, petechial hemorrhages). The incidence of these observations was similar in all groups and are presented in the table below. Findings are reported as % litters affected (no. of litters).

Concentration (ppm)	0	10,000
Gross		
Runts	8.7 (2)	21.1 (4)
Small subcutaneous hematomas	30.4 (7)	42.1 (8)
Petechial hemorrhages	17.4 (4)	5.3 (1)
Soft Tissue		
Hydronephrosis	17.4 (4)	26.3 (5)
Hydrocephaly	4.3 (1)	0 (0)
Skeletal		
Delayed ossification of 1 or more sternebrae	65.2 (15)	57.9 (11)
14^{th} rud. rib(s) or spur(s)	100 (23)	100 (19)
Wavy ribs	43.5 (10)	26.3 (5)
Bipartite thoracic centra	13.0 (3)	10.5 (2)

Inhaled HCFC-123 produced mild, transient sedation of mothers. All other parameters of pregnancy outcome and fetal development were similar to those of the control. HCFC-123 was not embryotoxic or teratogenic.

Reference: DuPont Co. (1976). Unpublished Data, Haskell Laboratory Report No. 227-76 (also cited in TSCA Fiche OTS0000695, OTS0530605, OTS0540605, OTS0544428, OTS0520876,

and OTS0555314).

Kelly, D. P. et al. (1978). Toxicol. Appl. Pharmacol., 45(1):293 (Abstract No. 170).

Reliability: Medium because a suboptimal study design was used in which only two dose levels were employed.

Additional References for Developmental Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Allied Chemical Corp. (1977). Unpublished Data, Industrial Biotest Laboratories, Inc. Report No. IBT No. 8562-09344.

Bio/dynamics (1989). Unpublished Data, Project No. 88-3303, April 24 (also cited in TSCA Fiche OTS0570913).

5.4 Reproductive Toxicity

Species/Strain:	Rats/Crl:CD®(SD)BR VAF/Plus strain
Sex/Number:	F_0 generation: 32 animals/sex/group F_1 generation: 28 animals/sex/group
Route of Administration:	Inhalation
Exposure Period:	F_0 generation: from 6 weeks of age through weaning of all litters (a total of at least 23 weeks of treatment) F_1 generation: from 4 weeks of age through weaning of all their litters (a total of approximately 28 weeks of treatment)
Frequency of Treatment:	6 hours/day, 7 days/week
Exposure Levels:	0, 30, 100, 300, 1000 ppm
Method:	In a two-generation reproduction study, groups of 32 male and 32 female rats (F_0) were exposed to 0, 30, 100, 300, or 1000 ppm HCFC-123. Rats in the F_0 generation were 4-weeks-old upon arrival. Animal room controls for temperature and humidity were set at 20ºC and 55%, respectively, and lighting was controlled to give 12 hours light and 12 hours dark. During the premating period, male and females were housed separately, 4 to a cage. During the mating period, animals were housed on the basis of 1 male to 1 female. At the end of the mating period, the males were rehoused with their former cagemates and the females were housed in individual breeding cages. All animals were given free access to pelleted diet and tap water.

The inhalation chambers used had a nominal internal volume of approximately 2.43 m^3. During operation, filtered, temperature and humidity controlled air was supplied to the chambers by an air handling unit. The volume flow of air to the chambers was monitored and recorded. During exposure, the animals were held in stainless steel mesh cages. A cage had 10 compartments; each compartment held one rat. Cages were evenly distributed on 5 levels within a chamber and cage positions were altered on a weekly basis. Liquid HCFC-123 was forced from a reservoir (under pressure with nitrogen) through metering values into copper coils where evaporation took place. The vapor was mixed with diluent air at 25 L/min and carried to the air entry points of the inhalation chambers. Information of the environment within each inhalation chamber was collected at 6 minute intervals during each 6-hour exposure. Airflow, temperature, relative humidity, and analyzed concentration were collected.

The F_0 generation was exposed to treatment from 6 weeks of age through to weaning of all litters. The F_1 generation was derived from litters of the F_0 generation. F_1 animals were directly exposed to the test material from 4 weeks of age through to weaning of their litters. For both generations, animals were mated at approximately 16 weeks of age. Due to differences in age at commencement of treatment, F_0 animals received 10 weeks of treatment prior to mating. F_1 animals received 12 weeks of treatment prior to mating. From presumed day 20 of gestation through to Day 4 post-partum females remained in their breeding cages and were allowed to deliver their young and to establish lactation without exposure to the test substance. Exposures were re-introduced on day 5 postpartum.

Vaginal smears were taken daily, prior to exposure, for the 7 days before, and during the 20-day mating period, to enable the number of animals that mated on specific days to be determined. This data was used to determine whether or not pregnancy occurred, to detect marked anomalies of the estrus cycle, to determine, where possible, day 20 of pregnancy, and to determine the mean pre-coital time and duration of pregnancy of dams that littered.

Twenty rats/sex/group of the F_0 generation were sacrificed after the weaning of all litters (a total of at least 23 weeks of

treatment). The remaining 12 animals/sex/group (designated as geriatrics, F_{0g}) were retained and sacrificed after 39 weeks of treatment.

On day 4 post-partum, pups were weighed and where possible, the litter was standardized to a total litter size of 8 pups (ideally 4 male and 4 female), by random selection for each sex. No pups were culled from litters of 8 or less regardless of sex ratio. One male and 1 female pup of each litter in the group was selected by median body weight for organ weight analysis and preservation of tissues. In addition for the 0 and 1000 ppm groups, 1 weanling of each sex was also chosen by random selection. On Day 21 post-partum 1 male and 1 female pup in each of 28 litters per group were retained for further study. Selection of pups was made using computer-generated random number tables.

During the course of the study, food consumption, water consumption, body weight, and reproductive indices (copulation index, fertility index, pregnancy rate, gestation index) were measured. The onset of vaginal opening was monitored in all selected females from 28 days post-partum. The occurrence of cleavage of the balanopreputial skinfold was monitored in all selected males from 35 days post-partum.

Clinical pathology investigations occurred at 14 and 15 weeks of age and included 8 parameters for the males and females. In addition, male analysis included follicle stimulating hormone, luteinising hormone, estradiol, progesterone, and testosterone. Among females, fat determinations of milk were also made during the lactation phase. For the F_0 geriatrics, blood samples were obtained at 44 and 45 weeks of age.

Shortly after day 21, all excess pups were sacrificed and examined externally and internally for abnormalities.

Organ weight analysis of the reproductive organs and pituitary were performed on adults and selected weanlings. Weight analysis of the liver was performed on F_0 and F_1 adults and on selected F_2 weanlings. Histopathological examinations were confined to F_0 and F_1 adults and selected F_2 weanlings. Approximately 40 organs and/or tissues were preserved for possible analysis; however, histology was restricted to reproductive tract-associated tissues, liver, and

pancreas.

GLP: Yes

Test Substance: HCFC-123, purity at least 99.8%

Results: The inhalation exposure systems produced comparable results across the groups for airflow, temperature, and relative humidity. Mean air flow ranged from 652-658 L/min across the groups. Mean chamber temperature ranged from 20.5-21.4ºC and mean relative humidity ranged from 49-53% across the test groups. The chamber mean analyzed concentrations for the F_0 generation were 0, 30, 100, 298, and 1008 ppm and for the F_1 generation were 0, 30, 100, 299, and 1010 ppm for the 0, 30, 100, 300, and 1000 ppm groups, respectively.

Summaries of reproductive outcomes for the F_0 and F_1 generations are provided in the tables below:

F_0 Generation

Concentration (ppm):	0	30	100	300	1000
Copulation Index (%):	93.8	96.9	96.9	100.0	96.9
Fertility Index (%):	96.7	96.8	100.0	96.9	96.8
Gestation Length (days):	22.2	22.3	22.2	22.4	22.5
Implantation sites:	15.3	16.8	15.6	15.5	14.4
Pregnancy Rate (%):	90.6	93.8	96.9	93.8	93.8
Gestation Index (%):	100.0	100.0	100.0	96.8	100.0
Mean % Born Alive:	99.2	98.7	97.4	96.6	99.1
0-4 Day Viability (%):	99.0	97.4	98.0	98.9	98.8
Weaning Viability Index (%):	97.9	98.3	100.0	99.6	100.0
Sex Ratio (% males):	54.0	49.1	50.8	48.1	46.9

F_1 Generation

Concentration (ppm):	0	30	100	300	1000
Copulation Index (%):	89.3	96.4	100.0	100.0	100.0
Fertility Index (%):	96.0	100.0	96.4	96.4	92.9
Gestation Length (days):	22.3	22.1	22.4	22.2	22.1
Implantation sites:	15.7	15.3	15.1	14.3	13.1
Pregnancy Rate (%):	85.7	96.4	96.4	96.4	92.9
Gestation Index (%):	100.0	100.0	100.0	100.0	100.0
Mean % Born Alive:	97.3	98.8	98.4	99.5	98.6
0-4 Day Viability (%):	99.0	95.4	96.9	99.2	98.1
Weaning Viability Index (%):	96.9	99.0	99.1	99.5	100.0
Sex Ratio (% males):	51.0	46.8	51.7	51.0	56.1

There were no significant differences in mating or fertility indices in either generation. In terms of reproductive performance, the only adverse finding was of decreased implantation counts among F_1 females at 1000 ppm. From Day 14, a dose-related reduction in both litter and mean pup weights occurred at > 100 ppm in the F_1 litters. In the F_2 litters, a clear, significant dose-related effect on mean pup weight was observed from Day 7 onwards, with pup weights lower than controls at all exposure levels.

There were no clinical signs of reaction to treatment during exposure. While loading the animals into the exposure chambers, 1 F_0 male at 30 ppm and 1 F_1 male at 1000 ppm were reported as showing a brief convulsion. These single instances were not considered attributable to treatment.

There was a total of 7 mortalities during the study, 3 in the F_0 generation and 4 in the F_1 generation. In the F_0

generation, 1 male at 300 ppm was sacrificed during week 14 due to poor condition. Macroscopic findings of note included enlarged and swollen liver, enlarged spleen and adrenals, and enlarged and congested pancreatic lymph nodes. The remaining 2 animals (1 control male and 1 geriatric female at 1000 ppm) died during blood sampling procedures. In the F_1 generation, 1 male at 30 ppm was sacrificed as a consequence of a damaged eye following blood sampling procedures, 1 male at 100 ppm was sacrificed at week 22 due to ulceration of a subcutaneous mass, and 2 females at 30 ppm were sacrificed following parturition due to poor condition. Both of these females had dead pups present in the uterus. Of these mortalities, the only one considered possibly associated with treatment was the F_0 male at 300 ppm with an enlarged liver.

Retarded weight gains were observed in the F_0 and F_1 animals which received 1000 ppm, and the F_0 males at 100 and 300 ppm. Retarded weight gains were observed during week 3 of pregnancy for the F_0 1000 ppm females and throughout pregnancy for the 1000 ppm F_1 females. Increased food intake occurred in the 300 and 1000 ppm F_0 males and females. Decreased food intake was noted during lactation in the F_0 and F_1 300 and 1000 ppm females and during days 4-6 of lactation in the 100 ppm F_1 females. Impaired food utilization occurred in the 1000 ppm F_0 males and females, the 1000 ppm F_1 females, and the 300 ppm F_0 females. Increased water intake occurred in the 300 and 1000 ppm F_0 males and females and in the 100 ppm F_0 females. All of these findings were attributed to treatment with HCFC-123.

There was no obvious difference apparent in the pre-mate vaginal smears for either generation. For both generations, there were no obvious treatment-related effects on mating performance, as assessed by the cell type in the vaginal smear on the day of conception or in the median pre-coital time. Pregnancy rate was high for all treated groups for both generations, at 92%.

Decreased triglycerides occurred in the 300 and 1000 ppm F_{0g} and F_1 males and females, in the 100 ppm F_{0g} females, and in the 100 ppm F_1 males and females. Decreased very low density lipoprotein (VLDL) was noted in the 1000 ppm F_0, F_{0g}, and F_1 males and females, in the 300 ppm F_0 and F_1 males and females, in the 100 ppm F_0, F_{0g}, and F_1 females,

and in the 30 ppm F_{0g} and F_1 females. The cholesterol profile of the 300 and 1000 ppm F_0, F_{0g}, and F_1 females was decreased, as well as in the 100 ppm F_0 females. The cholesterol profile of the 1000 ppm F_0 and F_{0g} males, the 100 and 300 ppm F_0, F_{0g}, and F_1 males, and the 30 ppm F_0 males appeared increased. All of these findings were attributed to treatment with HCFC-123.

Among the F_0 males at 14 weeks of age, LH values were slightly, but significantly, higher than controls at 300 and 1000 ppm. Among the F_0 geriatrics, there were no significant differences. Among the F_1 males, progesterone levels were slightly, but significantly, lower at 100 ppm and above. As there was neither persistent nor consistent pattern in the hormonal assays, the significant differences in LH and progesterone values were not considered attributable to treatment.

There was no suggestion in the values obtained from the CCK assay of an effect on treatment.

There was no obvious effect of treatment on milk fat content in either generation.

The mean age of occurrence of balanopreputial skinfold cleavage was slightly delayed among males at 300 and 1000 ppm compared with controls. The group mean body weight at attainment of sexual maturity was comparable to controls, suggesting differences in growth rate may have been a factor in the delay of sexual maturation. There was no obvious effect on the age of attainment of cleavage at 30 and 100 ppm.

There was no obvious effect on the mean age of attainment of vaginal opening.

In the F_0 generation, there were 2 instances of total litter loss: 1 female at 300 ppm was a total resorption and 1 female at 1000 ppm was a total litter loss in the post-partum phase. In the F_1 generation, there were 3 total litter losses all in the post-partum phase: 2 at 30 ppm and 1 at 300 ppm. As there was a low incidence of losses and no evidence of a strict dosage relationship, these losses were considered coincidental.

The 100, 300, and 1000 ppm F_0 and F_1 males and females,

and the 30 ppm F_0 males and females had increased liver weights. Macroscopic changes in the liver with associated microscopic changes of centilobular hepatocyte enlargement and vacuolation was found in the 300 and 1000 ppm F_0 and F_1 males and females. At 100 ppm, microscopic changes limited to centilobular hepatocyte enlargement/swelling occurred in the F_1 animals. Liver glycogen content was decreased in the 1000 ppm F_0 and F_1 animals. All of these findings were attributed to treatment with HCFC-123.

Exposure to HCFC-123 was principally associated with effects on growth and on the liver. Retarded weight gains were observed among directly exposed adults as well as among offspring during the pre-weaning period when direct exposure was confined to the lactating parent female. In terms of effects on the liver, slight changes were seen in some biochemical parameters among animals exposed at 30 ppm. Liver weights were increased at 30 ppm, but only among the F_0 animals. Histological changes appeared confined to exposures of 100 ppm and above. It was not possible to identify a no-effect level as effects were seen in some parameters at the lowest exposure level. In terms of reproductive performance, the only adverse finding was of decreased implantation counts among F_1 females at 1000 ppm. In terms of development, all exposure levels of HCFC-123 were associated with impaired pup growth in the offspring of the F_1 generation.

Reference: Huntingdon Research (1994). Report ALS 5/932336 (also cited in TSCA Fiche OTS0530498-4 and Malinverno, G. et al. (1996). Fundam. Appl. Toxicol., 34(2):276-287).

Reliability: High because a scientifically defensible or guidelined method was used.

Additional References for Reproductive Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Allied Signal (1994). Unpublished Data, Huntingdon Research Centre Ltd. Report ALS 4/920200 (also cited in TSCA Fiche OTS0556832).

Fraunhofer Institute of Toxicology and Aerosol Research (1996). Unpublished Data, Report No. 95/9.

Data from these additional sources were not summarized because the study

designs were not adequate.

Buschmann, J. et al. (1996). Teratology, 53(5):25A and Allied Signal, 1996, Heinrich, U., Fraunhofer Institute of Toxicology and Aerosol Research, MA-RR-96-2320 (also cited in TSCA Fiche OTS0558932).

DuPont Co. (1997). Unpublished Data, Haskell Laboratory Report HL-1997-00152.

DuPont Co. (1991). Unpublished Data, Haskell Laboratory Report No. 669-91 (also cited in TSCA Fiche OTS0528777, OTS0000695-11, OTS0530498, OTS0530498-1, OTS0543416, and OTS0530498-3, and Malley, L. A. et al. (1995). Fund. Appl. Toxicol., 25(1):101-114).

5.5 Genetic Toxicity

Type:	***In vitro* Bacterial Reverse Mutation Test**
Tester Strains:	*Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100
Exogenous Metabolic Activation:	With and without Arochlor-induced rat liver S-9
Exposure Concentrations:	0, 0.01, 0.02, 0.05, 0.1, 0.25, 0.5 mL liquid/vessel
Method:	This study followed the recommendations of OECD Guideline Number 471, "Genetic Toxicology: *Salmonella typhimurium*, Reverse Mutation Assay," OECD, Paris, August 1983 suitably modified for testing a volatile liquid. The mutagenicity assays were conducted using the *Salmonella* plate incorporation assay as described by Marion and Ames, 1983 with certain minor modifications to allow the testing of a volatile liquid. The sample of HCFC-123 was assayed twice, both in the presence and absence of a liver S-9 mix prepared from Arochlor 1254-induced Sprague Dawley rats. Three plates per dose were used in each experiment. In addition to the negative (zero exposure) controls, "absolute" negative controls were included in each test to confirm the spontaneous rates for the tester strains. The S-9 mix contained S-9 fraction, sucrose-tris-EDTA buffer, and co-factor solution. The co-factor solution contained Na_2HPO_4, KCl, glucose-6-phosphate, NADP (Na salt), and $MgCl_2$. In tests without metabolic activation,

the S-9 fraction was replaced with sucrose-tris-EDTA buffer. Treatments with activation were conducted by adding 0.5 mL of the S-9 mix to 0.1 mL of an overnight culture in a sterile bijou bottle. Two mL top agar was added. The force of addition was sufficient to mix the contents. The resulting mixture was then poured rapidly onto the surface of a prepared plate and allowed to gel. Plates were then placed inverted on stainless steel racks inside glass reaction vessels. A sterile cotton swab was placed on a lid at the top of each rack before the lid of the vessel was sealed. Appropriate volumes of HCFC-123 were added to the swab through a port in the lid, and the port was then immediately sealed. Each jar was incubated at 37ºC in the dark for 3 days before the plates were removed for counting.

Revertant colonies were counted using an automated electronic colony counter.

For each experiment, the positive control substances (assay) tested included acridine mutagen, 2-aminoanthracene, daunomycin HCl, 4-nitro-o-phenylenediamine, and N-methyl-N'-nitro-N-nitrosoguanidine. In addition to the "assay" positive controls, a sample of benzyl chloride was also tested as a positive control for the dosing regime used for volatile liquids.

A positive response in an individual experiment was achieved when 1 or both of the following criteria was met: a) a statistically significant dose-related increase in the number of revertant colonies was obtained; and b) a 2-fold or greater increase in the mean number of revertant colonies (over that observed for the concurrent negative control plates) which was statistically significant, was observed at least 1 dose level. A negative result was achieved when: a) there was no statistically significant dose-related increase in the mean number of revertant colonies per plate observed for the test compound; and b) in the absence of any such dose response, no increase in colony numbers was observed (at any test dose) which exceeded 2x the concurrent negative control.

GLP: Yes

Test Substance: HCFC-123, purity not specified

Results: Negative

Remarks: In 2 replicate experiments, no significant increases in revertant colony numbers were observed in any strain in either the presence or absence of an auxiliary metabolizing

system (S-9). In each case, toxic effects were observed at the highest exposure level tested (thinning of background level and/or reductions in colony numbers), indicating that this dose was an effective maximum.

In each experiment, the positive controls responded as expected, indicating that the assay was performing satisfactorily. Similarly, the protocol positive control, benzyl chloride, responded as expected, showing that the dosing regime used was appropriate for assaying a volatile liquid.

HCFC-123, therefore, gave an unequivocal negative, i.e. non-mutagenic response in all 5 strains of *S. typhimurium* both in the presence and absence of S-9, when tested to an exposure level which produced toxicity in each case.

Reference: ICI Central Toxicology Laboratory (1989). Report No. CTL/P/2421 (also cited in TSCA Fiche OTS0000695-3).

Longstaff, E. et al. (1981). Toxicol. Appl. Pharmacol., 72:15-31.

Marion, D. M. and B. N. Ames (1983). Mutat. Res., 113:173-215.

Reliability: High because a scientifically defensible and guidelined method was used.

Additional References for *In vitro* Bacterial Reverse Mutation Assay:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1976). Unpublished Data, Haskell Laboratory Report No. 581-76 (also cited in TSCA Fiche OTS0000695 and OTS0530604).

Allied Chemical Co. (1976). Litton Bionetics Report No. 2547, July 30 (also cited in TSCA Fiche OTS0000695).

Type:	***In vitro* Chromosome Aberration Test**
Cell Type:	Human lymphocytes
Exogenous Metabolic Activation:	With and without Arochlor-induced rat liver S-9
Exposure Concentrations:	0, 7.5, 15, 30% v/v for the 3-hour exposure with or without S-9 mix

0, 2.5, 5, 10% v/v for the 24-hour exposure without S-9 mix

Method: The procedures and experimental design employed complied with the recommendations of OECD Guideline 473.

Human lymphocytes, in whole blood culture, were stimulated to divide by addition of phytohaemagglutinin. After 48 hours of incubation, cultures were centrifuged, the supernatant removed and the cell pellet resuspended in culture medium (4.5 mL, or 4.0 mL for cultures subsequently to contain S-9). Freshly prepared S-9 was then added to the appropriate cultures. The cell suspensions were transferred to glass culture bottles with screw caps.

A preliminary test was performed to investigate the toxicity of HCFC-123 to dividing lymphocytes. Duplicate cultures were established in the preliminary test and for the main test, treatments were established in triplicate.

Treatment atmospheres were established by removal of an appropriate volume of air and injection of test material liquid on to the filter paper using a gas-tight syringe and needle inserted through the septum caps. Evaporation of HCFC-123 in the bottles at 37ºC generated treatment atmospheres of the required concentrations at atmospheric pressure. Untreated cultures contained an atmosphere of air, and an aliquot of positive control solution (chlorambucil or cyclophosphamide) was added to the relevant cultures. Treatment atmospheres were analyzed via gas chromatography.

HCFC-123 was tested in the main cytogenetic test for 3 hours with and without S-9 mix and for 24 hours without S-9 mix.

Three hours before the end of the incubation period, cell division was arrested by the addition of Colcemid®, cells were harvested, and slides prepared. One hundred metaphase cells per culture (or 300 per each treatment group) were examined for numerical (polyploidy) and structural chromosome damage. To examine the cytotoxicity of the test substance to dividing lymphocytes, approximately 1000 cells were scored and the mitotic index calculated.

GLP: Yes

Test Substance: HCFC-123, purity 99.95%

(19-December-2001)

Results: Positive

Remarks: The achieved concentrations were close to those intended in each case. Only 1 culture, intended to contain a 10% atmosphere for 24 hours, lost a significant amount of the test vapor during the treatment period (because the seal on the syringe needle inserted through the screw cap was accidentally dislodged).

In the absence of S-9 mix, exposure to HCFC-123 for 3 hours produced reductions in mean mitotic index (compared to untreated control values) of 28 and 59% at concentrations of 15 and 30%, respectively. At 7.5% no such evidence of toxicity was observed.

In the presence of S-9 mix, exposure to HCFC-123 produced a reduction in mean mitotic index of 57% at a concentration of 30%, but no relevant reductions at 7.5 or 15%.

Exposure to HCFC-123 for 24 hours in the absence of S-9 mix produced reductions in mean mitotic index of 20 and 64% at concentrations of 5 and 10%, respectively, but no relevant reductions at 2.5%.

Exposure to HCFC-123 for 3 hours in the absence of S-9 mix produced minor, but statistically significant increases in the frequency of aberrant metaphases at concentrations of 7.5 and 30% ($p<0.05$ and $p<0.01$, respectively), but only when gaps were included in the analysis. The biological significance of gap-type aberrations is not clear and HCFC-123 was not considered clastogenic on this evidence alone. A large, dose-related, increase in the number of polyploid cells was also observed. It is noted, however, in the study report that these data were derived by recording the number of polyploid cells observed while scanning the slide during chromosome analysis; the percentage of polyploid cells in each culture could not, therefore, be accurately determined and these data should thus be treated with caution.

Exposure to HCFC-123 for 3 hours in the presence of S-9 mix produced dose-related, biologically and statistically significant increases in the frequency of aberrant metaphases at a concentration of 30%, both including and excluding gaps ($p<0.001$ in each case). An increase in the number of polyploid cells was also observed in cultures exposed at 30%.

	Exposure to HCFC-123 for 24 hours in the absence of S-9 mix produced dose-related, biologically and statistically significant increases in the frequency of aberrant metaphases at all concentrations tested, both including and excluding gaps ($p<0.01$ at 2.5% and $p<0.001$ at 5 and 10%). No effect on the number of polyploid cells was observed under these conditions. The cytogenetic analyses of the 2.5% and 10% treatment groups were based on two cultures with a total of 200 metaphase cells, respectively. The known clastogens, cyclophosphamide and chlorambucil, induced significant increases in the frequency of aberrant metaphases compared to vehicle control values ($p<0.001$ in both cases).
Reference:	Life Sciences Research (1991). Unpublished Data, Report 91/0125 (also cited in TSCA Fiche OTS0555645 and OTS0570891).
Reliability:	High because a scientifically defensible and guidelined method was used.

Additional References for *In vitro* Clastogenicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

ICI (1990). Unpublished Data, Report CTL/P/2978.

Allied Signal (1991). Unpublished Data, Life Sciences Research Report 91/0093, July 18.

Type:	***In vivo* Mouse Micronucleus Assay**
Species/Strain:	NMRI Mouse/Hoe: NMRKf (SPF71)
Sex/Number:	Male and female/15 per sex per concentration
Route of Administration:	Inhalation (head and nose exposition)
Concentrations:	0, 0.2, 0.6, 1.8 vol. % (2000, 6000, 18,000 ppm)
Method:	The study was performed according to the EPA guideline, *In vivo* mammalian bone marrow cytogenetic tests: micronucleus assay, "HG-Chromo-Micronuc," August 1982, and takes into consideration the proposals and recommendation given in the EPA Gene Tox program 1983 (Mutat. Res., 123:61-118). Male and female mice were treated in a single inhalation exposure of 6 hours, and animals were sacrificed at 24, 48,

or 72 hours after inhalation. Five animals/group were sacrificed at each time period. Animals were 7 weeks of age at the start of the test. Male mice weighed 26-35 grams and female mice weighed 20-30 grams. Animals were housed in fully air-conditioned rooms in Macrolon cages, on softwood granulate in groups of 5 animals. Room temperature was maintained at 22±2ºC with a relative humidity of 55±10%.

For exposures, mice were placed individually in cylindrical plastic tubes and exposed to the specified gas concentrations in such a way that only the noses of the animals were inside the chamber. The chamber itself consisted of a stainless steel and glass cylinder with a volume of 60 L. HCFC-123 was applied to an evaporation unit at a constant speed by mean of a continuous infusion apparatus. In order to prevent evaporation of the test substance, the syringe filled with HCFC-123 was cooled with frozen CO_2 during the exposure. HCFC-123 was evaporated at 80ºC and diluted with air, yielding a volume of 600 L/hour. The mixture of test substance and air was introduced into a round-bottom mixing flask and diluted with an additional 200 L air/hour, resulting in a total volume of 800 L/hour. In order to ensure good mixing of the test substance with air, the flask was filled with small glass tubes. The mixture passed through a glass tube into the inhalation exposure chamber. During the exposures, CO_2, O_2, relative humidity, and temperature were measured. In order to determine the exact quantity of HCFC-123 in the exposure chamber, analytical examinations were performed using a one-beam-photometer.

During the exposures, the behavior of the animals was carefully observed and recorded.

At the specified times, the animals were sacrificed. Both femora were removed and the bones freed of muscle tissue. The proximal ends of the femora were opened and the bone marrow flushed into a centrifuge tube containing fetal bovine serum. A suspension was formed, centrifuged for 5 minutes and almost all the supernatant was discarded. One drop of thoroughly mixed sediment was smeared on a slide and air-dried for approximately 24 hours. The slides were stained with Giemsa. One thousand polychromatic erythrocytes (PCEs) were counted for each animal. The number of cells with micronuclei (MNPCEs) was recorded. In addition, the ratio of polychromatic to normochromatic erythrocytes (NCEs) was determined. All bone marrow

smears were coded to ensure that the group to which they belonged was unknown to the investigator.

Endoxan® was used as a positive control and was administered in a single inhalation period over 2.5 hours (2.5 mg/L air). Animals treated with the positive control were sacrificed 24 hours after administration.

The concentration levels were selected on the basis of a preliminary study in which administration of 2.5 vol. % caused partial lethality in male mice. The highest sublethal dose of 1.8 vol% was selected for the main study.

GLP: Yes

Test Substance: HCFC-123, purity approximately 100%

Results: Negative

Remarks: The mean nominal concentration of HCFC-123 measured for the male groups were 1860, 5650, and 17,660 ppm for the 2000, 6000, and 18,000 ppm groups, respectively. The mean nominal concentration of HCFC-123 measured for the female groups were 1870, 5720, and 16,880 ppm for the 2000, 6000, and 18,000 ppm groups, respectively.

All animals survived inhalation of HCFC-123. The following signs of toxicity were observed: irregular breathing (0.2, 0.6, and 1.8 vol. %), uncoordinated gait (0.6 vol. %), reduced spontaneous activity (1.8 vol. %), ataxic gait (1.8 vol. %), abdominal position (1.8 vol. %), slow respiration (1.8 vol. %), and anesthesia (1.8 vol. %). All animals were free of clinical signs of toxicity at 24 hours after inhalation. Most of the animals of all treatment groups showed lobular pattern of the liver upon sacrifice and dissection.

The incidence of MNPCEs of the animals treated with HCFC-123 was within the normal range of the negative control. The number of NCEs containing micronuclei was not increased. The ratio of PCEs/NCEs in both male and female animals remained unaffected by the treatment with HCFC-123 and was not statistically different from the control values.

Endoxan® induced, in both males and females, a marked statistically significant increase in the number of MNPCEs, indicating the sensitivity of the system. The ratio of PCEs to NCEs was not changed to a significant extent.

Reference: Hoechst (1988). Unpublished Data, Report No. 881340,

Study No. 88.0372 (Sept. 15) (also cited in TSCA Fiche OTS0000695-7 and OTS0570978).

Reliability: High because a scientifically defensible and guidelined method was used.

Type: ***In vivo*** **Unscheduled DNA Synthesis**
Species/Strain: Rats/Alderley Park (Alpk:APfSD)
Sex/Number: Male/5 per exposure level
Route of Administration: Inhalation (whole body)
Concentrations: 0, 8000, 12,500, 20,000 ppm
Method: The assay was designed to measure repair or unscheduled DNA synthesis (UDS) in cultured rat hepatocytes derived from animals exposed *in vivo*. The method was essentially that of Mirsalis and Butterworth, 1980 as modified by Ashby et al., 1985; 1987.

Rats were treated at 3 dose levels, 8000, 12,500, and 20,000 ppm. The top dose was estimated to be the maximum tolerated dose for HCFC-123 as determined from a preliminary toxicity assessment using dose levels of 30,000, 40,000, and 50,000 ppm. Positive (N-nitrosodimethylamine (NMDA)) and negative (air) controls were employed in each experiment.

Test atmospheres were generated using jacketed glass condensers heated to 45ºC using circulating water baths. HCFC-123 was delivered to the top of the condenser columns via pumps and flowed down against a counter-current of air. Test substance flow rates were adjusted accordingly to produce the required target atmospheric concentrations. The resultant vapor was then carried to individual exposure chambers by addition of clean dried air to a flask at the base of each condenser columns at a flow rate of 25 L/min. Test atmospheres were analyzed via gas chromatography. Temperature and relative humidity within each chamber were measured.

Animals were exposed whole body in chambers (internal volume approximately 100 L) for 6 hours. Two hours before the end of the inhalation exposure, the positive control animals were removed from the chambers momentarily, and were given a single oral 10 mg/kg dose of NMDA, by gavage. After dosing the animals were returned to the chambers for the remainder of the exposure period.

Two experiments were conducted. A total of 5 animals were exposed at each exposure level; 2 animals in one experiment and 3 animals in the other. A total of 2 positive and 2 negative control animals were included in each experiment, and only 1 of each was scored for induction of UDS.

Clinical observations of the animals was carried out during exposure and also immediately prior to perfusion.

Freshly isolated hepatocytes derived from treated males were cultured in the presence of tritiated thymidine and subsequently examined for UDS by autoradiography. Hepatocytes were prepared from treated animals by a 2-stage collagenase perfusion technique. Hepatocyte cultures were prepared by allowing cells to attach to plastic coverslips. Medium was removed and replaced with fresh medium containing ^{3}H thymidine. After 4 hours incubation at 37°C, the medium was removed, cells washed 3 times, and the cultures incubated overnight with medium containing an excess of unlabelled thymidine. Cultures were fixed and coverslips mounted onto microscope slides. Slides were coated with photographic emulsion and left for 14 days at 4°C in the dark. The emulsion was developed, fixed, and the cell nuclei and cytoplasm stained with Meyers haemalum and eosin Y phloxine. Slides were examined microscopically for signs of undue cytotoxicity. Coded hepatocyte preparations were examined for the induction of UDS using a microscope-mounted image analyzer. The number of silver grains over the nucleus was determined. An equivalent area of cytoplasm tangential to the nucleus and with the highest apparent number of silver grains was scored. The difference between these values was the net nuclear grain count. Sixty cells were scored from each animal.

A negative response was obtained where the mean net nuclear grain count of all treated animals was less than 0. The occurrence of a mean net nuclear grain count of 0 or greater was taken as indicative of a UDS response.

GLP: Yes
Test Substance: HCFC-123, purity 99.933%
Results: Negative
Remarks: Mean HCFC-123 concentrations for each group were within 20% of the target. In experiment 1, the mean analyzed concentrations were 7190, 12,300, and 18,500 ppm for the 8000, 12,500, and 20,000 ppm groups, respectively. In

experiment 2, the mean analyzed concentrations were 7320, 11,400, and 16,700 ppm for the 8000, 12,500, and 20,000 ppm groups, respectively. Within the chambers, the temperature ranged from 19.0-21.8ºC and the relative humidity ranged between 27-60%.

Animals exposed to 8000, 12,500, and 20,000 ppm HCFC-123 showed exposure-related clinical signs consistent with CNS depression (i.e. respiratory depression and reduced locomotor activity). With increase in atmospheric concentration, the onset of these effects became more rapid and animals exposed to 20,000 ppm were comatose after approximately 1.5 hours of exposure. One animal exposed to 20,000 ppm died after about 4.5 hours. The other concurrently exposed animal recovered, but was subdued and exhibited piloerection prior to perfusion. In experiment 2, all 3 animals from the top exposure group awoke after exposure, but were subdued prior to perfusion. Animals at the 8000 and 12,500 exposure levels were fully recovered before perfusion.

No apparent signs of cytotoxicity were observed in hepatocyte audioradiograms prepared from animals exposed to HCFC-123. Therefore, hepatocytes from the 2 highest exposure levels, 12,500 and 20,000 ppm were assessed for UDS. Examination of the mean net nuclear grain count and percentage of cells in repair showed that HCFC-123 did not induce DNA repair, as measured by UDS, at either exposure level. Hepatocytes from HCFC-123-treated animals had mean net nuclear grain values of less than 0.

Results from the negative and positive control treatments gave the appropriate responses.

Reference: Zeneca (1993). Central Toxicology Laboratory Unpublished Data: Report CLT/P/3807 (also cited in TSCA Fiche OTS0538133).

Ashby, J. et al. (1985). Mutat. Res., 156:1-18.

Ashby, J. et al. (1987). Mutagenesis, 2(6):489-490.

Mirsalis, J. C. and B. E. Butterworth (1980). Carcinogenesis, 1:621-625.

Reliability: High because a scientifically defensible and guidelined method was used.

(19-December-2001)

Type:	***In vivo* Chromosome Aberration**
Species/Strain:	Rats/Sprague Dawley
Sex/Number:	Male/10 per exposure level
Route of Administration:	Inhalation
Concentrations:	0, 300, 1000, 5000 ppm
Method:	Male rats, housed at Huntingdon Research Centre (HRC), were bled following exposure to the test chemical or negative control agent (6 hours/day, 7 days/week for 14 weeks). Approximately 2 mL of blood was taken from each rat via the orbital sinus vein and dispensed into a culture tube containing sodium heparin. Tubes were agitated for at least 1 minute, then held at ambient temperature prior to collection, during transportation to Hazelton Microtest, and prior to establishment in culture. A concurrent positive control group of 5 male rats were dosed intraperitoneally with 20 mg/kg cyclophosphamide (CPA) at Hazelton Microtest. These animals were bled 6 hours later on the same day that animals were sampled at HRC. Two blood cultures were established for each animal from all treatment and control groups. Cultures contained 1 mL of washed blood, Hepes-buffered medium containing fetal calf serum, and gentamycin. Phytohaemagglutinin was included in the culture medium to stimulate the lymphocytes to divide. Cultures were rocked continuously during incubation, and harvested 49 hours following initiation. Colchicine was added 1.5 hours prior to harvest to arrest dividing cells in metaphase. Slides were prepared and stained with Giemsa stain. Fifty metaphases were analyzed per culture for negative and positive control animals and animals receiving 5000 ppm HCFC-123. Mitotic indices based on a total of 500 cells per culture were determined. The test chemical was considered to be clearly positive if statistically significant increases in the proportion of cells with structural aberrations occurred at 1 (or more) concentration(s). Cells with exchange aberrations or cells with greater than 1 aberration occur very infrequently in negative control cultures. Their appearance was therefore to be considered of biological significance.
GLP:	Yes
Test Substance:	HCFC-123, purity not specified
Results:	Negative
Remarks:	When the data from all animals in each group were pooled, fewer cells with aberrations were apparent in the group

	receiving 5000 ppm HCFC-123 than in the concurrent negative control group. The decrease was small, but statistically significant. There was no evidence of a reduction in mitotic index in any 5000 ppm HCFC-123-treated animal. A clear statistically significant increase in cells with aberrations was seen in cultures from rats receiving CPA.
Reference:	Allied Signal (1992). Unpublished Data, Sponsor Study No. ALS/4-R, Hazelton Study No. ASU 1/RLC, Hazelton Report 1RLREASU.001.
Reliability:	High because a scientifically defensible and guidelined method was used.

Additional References for *In vivo* Genetic Toxicity: None Found.